Modelling the Neuropsychopharmacology of Obsessive-Compulsive Disorder in the Common Marmoset (*Callithrix jacchus*)

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For my mother

Abstract

This thesis extends the understanding of the neural and neurochemical contributions to two forms of behavioural adaptation, reversal learning and contingency degradation, in which stimulus/action–reward contingencies are altered. The results are interpreted within the psychological framework of the compulsivity construct, and their implications for the pathological behaviour of obsessive-compulsive-disorder (OCD) are considered.

The orbitofrontal cortex (OFC) and striatum are key brain structures involved in reversal learning, as are the neurotransmitters serotonin (5-hydroxytryptamine, 5-HT) and dopamine (DA) within those respective regions. However, there has been little empirical evidence of how these two structures and neurochemical systems interact, especially in the functional context of reversal learning. In Chapter Three, the impact of experimentally-induced reductions of 5-HT in the anterior OFC on monoamine levels in subcortical structures such as the striatum and amygdala was determined, DA being found to be significantly up-regulated in the amygdala. Functionally, 5-HT depletion of the OFC has previously been shown to induce deficits in reversal learning. To determine the possible causal significance of amygdala dopamine up-regulation for said reversal learning deficit, the effects of blocking the upregulation with the infusion of intra-amygdala DA receptor antagonists following bilateral OFC 5-HT depletion were investigated in a reversal learning paradigm.

In Chapter Four, the differential roles of regions of striatum were examined in visual reversal learning. Two recent investigations in non-human primates highlighted the role of the striatum in reversal learning, but pinpointed the critical region to be either the ventromedial caudate or the putamen. Marmosets were trained on a serial reversal task that allowed multiple acute neural manipulations, and the ventromedial caudate and putamen were then reversibly inactivated using the $GABA_A$ agonist muscimol. Results indicated dose-related impairments specifically in reversal learning within the putamen, with sparing of discrimination retention. By contrast, similar reversible inactivation of the caudate nucleus produced marked deficits in visual discrimination performance (retention).

In Chapter Five, the neural basis of action–outcome contingency knowledge was investigated by inactivating distinct regions of the PFC, the perigenual ACC (pgACC; area 32) and the anterior OFC, and determining response sensitivity to the degradation of action–outcome contingencies. In previous work, excitotoxic lesions of either the pgACC or the OFC had been found to induce insensitivity to contingency degradation in marmosets. However, the design of that experiment did not allow specification of whether stimulus– or action–outcome associations were disrupted, and a precise neural locus could not be determined for the behavioural effects as the OFC lesions included parts of the lateral and medial OFC. I therefore developed a novel contingency degradation paradigm that distinguished between stimulus– and action–outcome associations to enable the study of acute pharmacological manipulations in both brain regions. The pgACC and OFC were reversibly inactivated using GABAA–$GABA_B$ agonists (muscimol–baclofen). Whereas the pgACC inactivation produced selective deficits in sensitivity to action–outcome

contingency degradation, OFC inactivation reduced the suppressive effect of noncontingent reward on responding more generally but left intact sensitivity to degradation of the contingencies.

These results are discussed in terms of different theories of the functions of the pgACC and OFC. In the final discussion the findings on the neural substrates of reversal learning and contingency degradation are drawn together in terms of their significance for theories of PFC involvement in cognitive control, and for the understanding of OCD and other neuropsychiatric disorders.

Preface

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University of similar institution. It does not exceed the prescribed word limit for the Biology Degree Committee.

I am indebted to many people for their help in the experiments of this thesis, in particular my collaborators Nicole Horst and Naotaka Horiguchi. Nao was responsible for the training of several animals and a substantial amount of data collection in Chapter 5. Nicole trained me in working with the marmosets, conducted the stereotactic surgeries, worked closely in an advisory capacity to mediate data collection and also contributed to animal training and data collection. I was in receipt of an MRC-BCNI studentship, and my experiments were funded by a Wellcome Trust Senior Investigator Award 104631/Z/14/Z to Trevor Robbins, and conducted within the University of Cambridge Behavioural and Clinical Neuroscience Institute, supported by a joint award from the MRC and the Wellcome Trust.

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Research Assistant, is a generally excellent human being, and is always helpful whether the task at hand is anaesthesia monitoring or having a chat.

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My success has also been dependent on the support of my loving family, my father, Sue and my sister Shannon, who can always be turned to in times of difficulty. The same can be said of Heather Stallard and Tam Blaxter, my best friends who have faithfully supported me throughout the PhD. And finally I thank my partner Joe, whose support cannot be described or quantified, and whom I love very much.

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5,7-DHT	5,7-dihydroxytryptamine
5-HT	5-hydroxytryptamine, or serotonin
ACC	anterior cingulate cortex
ADHD	attention-deficit/hyperactivity disorder
ANOVA	analysis of variance
AP	anteroposterior
ATD	acute tryptophan depletion
BA	Brodmann Area
BD	bipolar disorder
CBT	cognitive and behavioural therapy
CSTC	cortico-striato-thalamo-cortical
DA	dopamine
dlPFC	dlPFC
DLS	dorsolateral striatum
DMS	dorsomedial striatum
DOPAC	3,4-dihydroxyphenylacetic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	diffusion tensor imaging
ERP	Exposure and Response Prevention
fMRI	functional magnetic resonance imaging
FR	fixed ratio
HPLC-ED	high-performance liquid chromatography with electrochemical detection
i.m.	intramuscular
ITI	intertrial interval
LM	lateromedial
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAA	N-acetylaspartate
NAc	nucleus accumbens
NACWO	Named Animal Care and Welfare Officer
NA	noradrenaline
NVS	Named Veterinary Surgeon
OCS	obsessive-compulsive symptoms
OFC	orbitofrontal cortex
PD	Parkinson's Disease

PET	positron emission tomography
PFC	prefrontal cortex
pgACC	perigenual anterior cingulate cortex
PTSD	Post-traumatic stress disorder
QoL	quality of life
s.c.	subcutaneous
SERT	serotonin transporter
SPECT	single-photon emission computed tomography
SSRI	Selective Serotonin Reuptake Inhibitor
VBM	voxel-based morphometry
vlPFC	ventrolateral PFC
vmPFC	ventromedial prefrontal cortex
VR	variable ratio
V	ventral
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

1 General Introduction

1.1 Overview

The theoretical framework for the experiments of this thesis was to model aspects of the neuropsychopharmacology of obsessive-compulsive disorder (OCD) in the common marmoset. The common marmoset, a new world monkey, was chosen as the model species due to the greater homology between its brain and that of a human, compared to the homology of a rodent. The introduction begins by providing background on OCD and its clinical relevance (§1.2), followed by a description of what is currently known of the neuroanatomical substrates of the disorder (§1.3). The psychology of OCD as a disorder of compulsivity is then considered (§1.4). The neural basis of two popular conceptualisations of compulsivity, cognitive inflexibility and an imbalance between the habitual and goal-directed action systems in the control of behaviour, are explored, using the paradigms of reversal learning and contingency degradation respectively. Investigations into the neural underpinnings of reversal learning and contingency degradation form the basis of chapters 4 and 5 respectively. Thus, the complex and multi-faceted trait of compulsivity was not modelled directly, instead select, well-defined psychological processes distal to the overall behavioural phenotype were examined. By breaking compulsivity down into small and manageable psychological elements it was hoped that it would be easier to identify underlying neural loci. Finally, the pharmacological understanding of OCD was examined in the introduction (§1.5), and this information, combined with that of the brain areas identified as regions of interest in OCD (§1.3), and in the reversal learning literature (§1.4.2.3), was the theoretical basis for the neurochemical investigation in chapter 3. Results pinpointing neurochemical interactions between OFC serotonin and amygdala dopamine, the role of the striatum in reversal learning, and the role of the OFC and pgACC in contingency degradation were gathered, findings which fit neatly with the evidence of abnormalities in these regions as part of the dysfunctional cortico-striato-thalamo-cortical circuitry of OCD.

1.2 Introduction to obsessive-compulsive disorder

1.2.1 Definition and nosology

Obsessive-compulsive disorder (OCD) is a chronic and debilitating neuropsychiatric disorder characterised by the presence of *obsessions* and *compulsions* (American Psychiatric Association 2013).

Obsessions are persistent, recurring thoughts and urges which occur despite being intrusive and unwanted by the individual, and induce distress and anxiety. Individuals attempt to ignore or suppress the thoughts, or to neutralise them by the performance of mental acts or physical actions, such as compulsions.

Compulsions are repetitive behaviours and mental acts that individuals feel driven to perform in response to an obsession or set of rules. They are intended to prevent or reduce anxiety or distress, or to avert a perceived dreaded situation from occurring, but are clearly excessive and/or are not realistically connected to that which they are designed to prevent.

Individuals can suffer from obsessions or compulsions, or most commonly both (Abramowitz et al. 2009), which induce substantial distress and impairment in functioning across social, occupational and family spheres. OCD has been ranked by the World Health Organisation as one of the top ten leading causes of disability worldwide (World Health Organisation 1999) and remains a significant social and economic burden on both individuals and their families, and also on society as a whole (Wittchen et al. 2011; DuPont et al. 1995; Knapp et al. 2000; Hollander et al. 1997; 2016). Insight from epidemiological studies over the last few decades has revealed OCD to be much more common than previously thought, with the disorder having been described as a "hidden epidemic" (Jenike 1989; Hollander 1997). OCD can affect adults and children from all cultures, ethnicities, genders and backgrounds and its manifestations are highly heterogeneous; the profile of the obsessions and compulsions of each patient vary greatly between individuals and have been described to "encompass the entire range of human thought and behaviour" (Pauls et al. 2014). While psycho- and pharmacotherapy can be effective in treating OCD in some patients, the treatment gap for OCD is very large (Kohn et al. 2004), and additionally patients and their families must deal with stigma concerning the condition in everyday life (Ociskova et al. 2013). In the fifth, most recent, edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), a chapter was devoted to the description of OCD and related disorders which share clinical features, which include body dysmorphic disorder, trichotillomania, excoriation (skin picking) disorder and hoarding disorder.

1.2.2 Epidemiology and demographic features

1.2.2.1 Epidemiology

Over the past few decades prevalence estimates for OCD have been in a state of flux. The influential US Epidemiologic Catchment Area (ECA) study (Robins and Regier 1991) in the late 1980s heralded a new era for psychiatric epidemiology, as structured diagnostic interviews were used for the first time, and on a large scale, to more reliably detect psychiatric disorders (WHO World Mental Health Survey Consortium 2004). A wave of studies then followed, applying the ECA template to populations in other countries and allowing the cross-national comparison of epidemiological data (Weissman et al. 1994; Horwath and Weissman 2000). The next significant development was the establishment by the WHO of a more sophisticated diagnostic interview, the Composite International Diagnostic Interview (CIDI) (Robins et al. 1988; Kessler et al. 1998), which was taken up in a second wave of studies. Researchers have since then continued to explore the epidemiology of OCD in new countries, under changing diagnostic criteria and social backdrops, and in subsets of populations stratified by age or ethnicity. Though the CIDI is the most common, a variety of diagnostic instruments continue to be used, and a host of other methodological differences between studies (Fontenelle et al. 2006; Regier et al. 1998) have led to a range of prevalence estimates for OCD (Horwath et al. 2011) which are difficult to compare and interpret (Weich and Araya

2004). Table 1.1 shows a selection of epidemiological studies in the general population, and Table 1.2 a selection of studies that stratified samples by age. As can be seen by the diversity of findings in Tables 1.1 and 1.2, figures fro the lifetime prevalence of OCD range from 0.1 to 6.7%.

The findings of the ECA study and those contemporaneous to it produced lifetime prevalence estimates of 2-3%, 50-100 times more common than previously thought, suggesting that OCD had been radically underdiagnosed in the community (Rasmussen and Eisen 1990; 1992, a; b; 1994), though low temporal stability of the diagnoses (Nelson and Rice 1997) and a lack of replication of the detection of OCD by lay interviewers were raised as concerns (Helzer et al. 1985; Anthony et al. 1985). In addition, it has been speculated that lifetime prevalence estimates might be underestimated due to the use of retrospective evaluations, which are susceptible to recall bias and memory distortions; one study found retrospective evaluation placed OCD prevalence at 0.7% whereas cumulative evaluation put the figure at 7.1% (Takayanagi et al. 2014).

Table 1.1. *Worldwide prevalence of OCD in general populations*

Study	Location	Sample size	Interviewers	Diagnostic instrument	Prevalence (%)			
					One month	Six month	One year	Lifetime
Myers et al. 1984 Robins et al. 1984 Karno et al. 1988	US*	18,572	Lay	DIS	0.4	1.5	1.6	2.5
Bland et al. 1988 Kolada et al. 1994	Canada*	3,258	Lay	DIS		1.6	1.4	2.9
Canino et al. 1987	Puerto Rico*	1,513	Lay	DIS			1.8	2.5
Lee et al. 1987	South Korea*	5,100	Lay	DIS			1.1	1.9
Henderson and Pollard 1988	US	497	Lay	ASI	2.8			
Hwu et al. 1989	Taiwan*	11,004	Lay	DIS			0.4	0.7
Wells et al. 1989 Oakley-Browne et al. 1989	New Zealand*	1,498	Lay	DIS			1.1	2.2
Faravelli et al. 1989	Italy	1,110	Trainee psychiatrists	SADS	0.63			0.72
Stefánsson et al. 1991	Iceland	862	Lay	DIS				2.0
Wittchen et al. 1992	Germany*	483	Lay	DIS			1.6	2.1
Chen et al. 1993	Hong Kong	7,229	Lay	DIS				0.87 (males) 1.22 (females)
Degonda et al. 1993 Angst et al. 2004 Angst et al. 2005a	Switzerland	591-367 (six inter-views)	Medical and psychological students	SPIKE			0.7	
Nestadt et al. 1994	US	767	Psychiatrists	SPE	0.3			

Worldwide prevalence of OCD in general populations (continued)

Study	Location	Sample size	Interviewers	Diagnostic instrument	Prevalence (%)			
					One month	Six month	One year	Lifetime
Jenkins et al. 1997	UK	10,108	Lay, with reappraisal by psychiatrists with SCAN	CIS-R then SCAN	1.6 ICD-10			
Stein et al. 1997	Canada	2,261	Lay, with reappraisal by researchers with SCID	CIDI	3.1 (CIDI) 0.6 (SCID)			
Almeida-Filho et al. 1997	Brazil	6,476	Medical students and health professionals	QMPA				0.7 (Brasília) 2.1 (Porto Alegre)
Bijl et al. 1998	Netherlands	7,076	Lay	CIDI	0.3		0.5	0.9
Wittchen et al. 1998	Germany	3,021	Trainee psychiatrists and researchers	CIDI			0.6	0.7
Henderson et al. 2000 Andrews et al. 2001 Crino et al. 2005	Australia	10,641	Lay	CIDI	0.5 DSM-III 0.3 ICD-10 0.5 DSM-IV		0.7 DSM-III 0.4 ICD-10 0.6 DSM-IV	
Grabe et al. 2000	Germany	4,075	Lay	CIDI			0.39	0.5
Kringlen et al. 2001	Norway	1,080	Mostly nurses, some sociology/psychology students	CIDI			0.7	1.6
Andrade et al. 2002	Brazil	1,464	Lay	CIDI	0.3 ICD-10		0.3 ICD-10	0.3 ICD-10
Çilli et al. 2004	Turkey	3,012	Trainee psychiatrists	CIDI			3.0 (2.2 ICD-10)	
Mohammadi et al. 2004	Iran	25,180	Clinical psychologists	SADS	1.8			

Worldwide prevalence of OCD in general populations (continued)

Study	Location	Sample size	Interviewers	Diagnostic instrument	Prevalence (%)			
					One month	Six month	One year	Lifetime
Jacobi et al. 2004	Germany	4,181	Non-clinical "mostly psychologists"	CIDI	0.4			0.7
Vicente et al. 2004 Vicente et al. 2006	Chile	2,978	Social sciences students	CIDI	1.2	1.2	1.2	1.2
Kessler et al. 2005b Kessler et al. 2005a	US	9,282	Lay	WMH-CIDI			1.0	1.6
Torres et al. 2006b	UK	8,580	Lay	CIS-R	1.1 ICD-10			
Gureje et al. 2006	Nigeria	4,984	Lay	WMH-CIDI			0.1	0.1
Kringlen et al. 2006	Norway	2,066	Psychiatric nurses	CIDI			0.3	0.6
Cho et al. 2007	South Korea	6,275	Lay	CIDI			0.6	0.8
Ruscio et al. 2010	US	2,073	Clinicians	WMH-CIDI			1.2	2.3
Adam et al. 2012	Germany	4,181	Psychologists and physicians	CIDI			0.7	
Viana and Andrade 2012	Brazil	5,037	Lay	WMH-CIDI				6.7
Subramaniam et al. 2012	Singapore	6,616	Lay	CIDI			1.1	3.0
Navarro-Mateu et al. 2015	Spain	2,621	-	CIDI	0.9		0.3	0.4
Guo et al. 2016[†]	China	2,621	Mixed	CIDI (5x) & SCID (3x)	0.9			3.17

Diagnostic criteria used were the version of the DSM in usage at the time, unless otherwise stated.

[*]Data were included in the cross-national analysis of Weissman et al. 1994. Data quoted are the figures from the original papers if given, or if not the re-analysed and adjusted values of Weissman et al.

[†]Meta-analysis of nine studies: Li et al. 2008, Ruan et al. 2010, Zhang 2010, Yu 2010, Chen 2012, Liu et al. 2013, Wang et al. 2013, Liu 2012, Li 2013. Meta-analysis used as most

studies were theses, unable to accessed, or Chinese language.
DIS - Diagnostic Interview Schedule (Robins et al. 1981)
ASI - Anxiety Symptoms Interview (Lane et al. 1990)
SADS - Schedule for Affective Disorders and Schizophrenia
SPIKE - Structured Psychopathological Interview and Rating of the Social Consequences of Psychic Disturbances for Epidemiology (Angst et al. 1984)
SPE - Standardized Psychiatric Examination. Developed specifically for Nestadt et al. 1994
CIS-R - Clinical Interview Schedule - Revised (Lewis et al. 1992)
SCAN - Schedules for Clinical Assessment in Neuropsychiatry (Wing et al. 1990)
CIDI - WHO Composite International Diagnostic Interview (Robins et al. 1988; Kessler et al. 1998)
QMPA - Questionário de Morbidade Psiquiátrica de Adultos
WMH-CIDI - World Mental Health Survey Initiative Version of the World Health Organization Composite International Diagnostic Interview (Kessler and Ustün 2004)

Table 1.2. *Worldwide prevalence of OCD in juvenile, young adult and older adult populations*

Study	Location	Sample size	Age range	Interviewers	Diagnostic instrument	Prevalence (%)			
						One month	Six month	One year	Lifetime
Flament et al. 1988	US	5,596	14-18	Mental health professionals	DICA	1.0			1.9
Lewinsohn et al. 1993	US	1,710	14-18	Psychologists or social workers	K-SADS	0.06			0.53
Reinherz et al. 1993	US	386	mean: 17.9	Lay	DIS	1.3		1.3	2.1
Valleni-Basile et al. 1994	US	3283	12-15	Psychiatrists	K-SADS	3.0			
Douglass et al. 1995	New Zealand	930	18	Psychiatrists	DIS			4.0	
Apter et al. 1996	Israel	861	16-17	Psychiatrists	STSOBS				2.3
Costello et al. 1996	US	4,500	9-13	Lay	CAPA		0.17 (3 month)		1.9
Verhulst et al. 1997	Netherlands	780	13-18	Lay	DISC-C & -P		0.9		
Canals et al. 1997	Spain	280	18	Lay	SCAN	0.7 (DSM-III-R) 1.4 (ICD)			
Steinhausen et al. 1998	Switzerland	1964	7-16	Undergraduate psychologists	DISC-P		0.2		
Maina et al. 1999	Italy	1883	17	Trainee psychiatrists	DIS	2.0			2.6
Heyman et al. 2001	UK	10,438	5-15	Lay	DAWBA				0.25

Worldwide prevalence of OCD in juvenile, young adult and older adult populations (continued)

Study	Location	Sample size	Age range	Interviewers	Diagnostic instrument	Prevalence (%)			
						One month	Six month	One year	Lifetime
Green et al. 2005	UK	7,977	5-16	Lay	DAWBA	0.2			
Suvisaari et al. 2009	Finland	1,863	19-34	Lay, reviewed by psychiatrists	SCID	0.38			0.65
Beekman et al. 1998	Netherlands	3,107	55-85	Lay	DIS		0.6		
Ritchie et al. 2004	France	1,873	65+	Nurses and psychologists	MINI	0.5			1.0
Préville et al. 2008 Grenier et al. 2009	Canada	2,798	65+	Health professionals	ESA-Q			1.5	

DICA – Diagnostic Interview for Children and Adolescents (Herjanic and Campbell 1977)
K-SADS – Schedule for Affective Disorders and Schizophrenia for School-Age Children (Chambers et al. 1985)
DIS - Diagnostic Interview Schedule (Robins et al. 1981)
STSOBS – Schedule for Tourette's Syndrome and Other Behavioral Syndromes
CAPA – Child and Adolescent Psychiatric Assessment (**Angold1995**)
DISC - Diagnostic Interview Schedule for Children, Child or Parent Version (Costello et al. 1985)
SCAN - Schedules for Clinical Assessment in Neuropsychiatry (Wing et al. 1990)
DAWBA - Development and Well-Being Assessment (Goodman et al. 2000)
SCID - Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al. 2002)
MINI - Mini International Neuropsychiatric Interview (Lecrubier et al. 1997; Sheehan et al. 1997)
ESA-Q - Enquête sur la Santé des Aînés computer-assisted questionnaire. Developed specifically for Préville et al. 2008.

Table 1.3. *Incidence of OCD*

Study	Location	Sample size	Diagnostic instrument	Follow-up duration (years)	One year incidence rate (%)
Eaton et al. 1989	US	10,861	DIS	1	0.69
Crum and Anthony 1993	US	13,306	DIS	1	0.79
Valleni-Basile et al. 1996*	US	488	K-SADS	1	0.7
Nestadt et al. 1998	US	1,920	DIS	13	0.12 0.055 DSM-III-R
De Graaf et al. 2002	Netherlands	5,567	CIDI	1	0.2 DSM-III-R

* Study of adolescents with mean age of 13 years.
Diagnostic criteria used were from DSM-III unless otherwise stated. Incidence rate is the number of new cases of OCD per 100 person-years, expressed as a percentage.
DIS - Diagnostic Interview Schedule (Robins et al. 1981)
K-SADS – Schedule for Affective Disorders and Schizophrenia for School-Age Children (Chambers et al. 1985)
CIDI - WHO Composite International Diagnostic Interview (Robins et al. 1988; Kessler et al. 1998)

The majority of epidemiological studies have examined the *prevalence* of OCD, a measure of the proportion of a population that has OCD over a certain timescale. Another common measure of disease frequency is *incidence*, the rate of new cases occurring within a population over a certain period of time. Prevalence estimates alone can indicate the total burden of OCD on society, but not the typical course or manifestation of the disorder (Coggon et al. 1997; Porta et al. 2014). Several groups have examined the incidence of OCD (Table 1.3), and as with the prevalence statistics, results are conflicting (Fontenelle et al. 2006), with reported one year incidence rates ranging between 0.05% and 0.79%.

OCD epidemiology in the elderly has been relatively understudied, compared to that of child and adolescent OCD. In the US cross-sectional sample studied in the National Comorbidity Survey-Replication (NCS-R), those in the 60+ age bracket were found to have the lowest OCD prevalence (0.7% cf. 2.3% of 30-44 year olds; Kessler et al. 2005a) while four studies which focussed solely on older adults also found lower prevalence than in the general population (Beekman et al. 1998; Ritchie et al. 2004; Préville et al. 2008; Grenier et al. 2009). However, prevalence in older adults may be underestimated, as most studies do not include those in residential care, where prevalence is thought to be higher (Junginger et al. 1993). OCD symptomatology is not thought to differ in older adults (Carmin et al. 2012), but diagnosis can be particularly challenging as individuals often present with comorbid mental and physical health problems (Calamari et al. 2012).

The majority of epidemiological surveys which have looked at OCD prevalence and incidence have been based in Western Europe, North America, Australia and New Zealand, with relatively few in Africa, South America, or Asia (Table 1.1 and 1.2)[1], and thus most of the data considered thus far has been sourced

[1] It should be noted that while I attempted to make Tables 1.1 and 1.2 as comprehensive as possible, they will still reject a bias towards Western Europe and North America as a consequence of more limited access to journals from outside these regions, and the limitation that only English-language studies have been included. The number of studies from Africa, South America and particularly from Asia are therefore likely to be underestimates.

from countries where people of colour (PoC) are in the minority. However, several Western studies have focussed specifically on the epidemiology of PoC, i.e. ethnic minorities in the West, most notably in the National Survey of American Life (NSAL; Jackson et al. 2004), which reported on the prevalence of mental illness in black Americans. Such studies are of interest both in order to examine psychiatric morbidity in these understudied ethnic groups, and to ascertain if there are interactions between belonging to a minority and the development of psychopathology.

Results from the NSAL gave one year and lifetime OCD prevalence statistics of 1.5% and 1.6% respectively for both African Americans and blacks of Caribbean descent (Himle et al. 2008), figures which were similar to those of 1.0% and 1.6% previously found in the general American population (Kessler et al. 2005b; a). The similarity of the one year and lifetime prevalences for the NSAL sample may suggest that OCD is particularly persistent within these groups, a result seen in a previous study with respect to a wide range of psychiatric disorders (Breslau et al. 2005). The average age of onset was also found to be higher than in other studies, which the authors suggest may be due to the increased influence of environmental factors in OCD aetiology (Himle et al. 2008). Another study conducted in the Los Angeles area in the US, found a much lower lifetime prevalence in Mexican Americans than in non-Hispanic white Americans (1.8% vs. 3.0%; Karno et al. 1987). Furthermore, datasets from general cross-sectional surveys which have been analysed with regard to ethnicity yield conflicting findings; any ethnicity other than non-Hispanic white was found to be a negative predictor of OCD in the ECA study (Karno et al. 1988), though Hispanics had the highest lifetime prevalence in the NCS-R (Breslau et al. 2006), whereas others have reported higher prevalence/incidence among black Americans or among ethnic minorities in the UK (Valleni-Basile et al. 1996; Heyman et al. 2001).

Other epidemiological studies have focussed on vulnerable groups such as the intellectually disabled, the homeless and refugees. These groups are often excluded from general epidemiological surveys (Wang et al. 2005), despite evidence that social adversity is associated with increased risk for psychopathology (Dohrenwend 2000). Two studies of intellectually disabled adults found point prevalences of 0.7% and 2.5%, with illness associating with lower ability among other factors (Cooper and Bailey 2001; Cooper et al. 2007). Studies within homeless populations report an increased prevalence of psychiatric illness in general, but there is a dearth of data on rates of OCD as many studies have a narrow focus on disorders such as substance abuse and psychotic illnesses (Ball et al. 2005). In the few studies which have examined OCD, startlingly high rates have been recorded, with figures of 19% point and 62% lifetime prevalence among homeless women in Canada (Strehlau et al. 2012) and a 19% point prevalence in homeless adults in Sydney (Taylor and Sharpe 2008). Similarly, the majority of epidemiological work on the mental health of refugees has been restricted to post-traumatic stress disorder (PTSD) and depression (Fazel et al. 2005), and is usually conducted within high-income countries, when the majority of refugees come to reside in low- and middle-income countries (Reed et al. 2012). However, limited evidence suggests that OCD affects adult and child refugees at a rate equal to or slightly higher than that of the general population (Steel et al. 2005; Bogic et al. 2012; Leth et al. 2015). The high prevalence of OCD within vulnerable populations highlights the need for further resources and study to be devoted to these groups.

1.2.2.2 Cross-cultural presentation

OCD is a global disorder widely regarded to be transcultural, with the core symptom dimensions (§1.2.3.1) transcending cultural boundaries (Staley and Wand 1995; Sasson et al. 1997; Silva 2006). Studies in Taiwan, Japan and Iran for example, found very similar structures of symptom dimensions to those consistently identified in Western studies (Juang and Liu 2001; Matsunaga et al. 2008; Asadi et al. 2016). However, OCD does not exist in a vacuum; obsessions of an individual often incorporate themes that are prevalent in their particular socio-cultural context. An example in the UK over the past few decades is the ebb of obsessions concerning asbestos contamination and the rise in those centred on HIV/AIDS (Silva 2006). Moreover, it has been theorised that the predominance of aggressive obsessions in Brazilian populations may be due to a rise in violent crime (Fontenelle et al. 2004).

Religion is the variable which appears to have the greatest impact on the differential manifestation of obsessional content across cultures, both in terms of which religions are prevalent in a region and the overall level of religiosity. The proportion of patients who experience religious obsessions appears to correlate with the religiosity of an area; a study in China, a country where only a small proportion of the population endorses a religion, found religious obsessions very infrequently (Li et al. 2009), whereas studies from majority Muslim or Jewish Middle Eastern countries found religious obsessions in a much higher proportion of patients (Mahgoub and Abdel-Hafeiz 1991; Okasha et al. 1994; Shooka et al. 1998; Ghassemzadeh et al. 2002; Greenberg and Witztum 1994; Greenberg and Gaby Shefler 2002). A high level of compulsive washing has also been found in these countries, where normal religious practice involves symbolic purifying rituals of cleansing before prayer (Okasha et al. 1994; Ghassemzadeh et al. 2002; Mahgoub and Abdel-Hafeiz 1991; Shooka et al. 1998; Greenberg and Gaby Shefler 2002). Others however, have failed to find a relationship between religiosity and religious obsessions (Tek and Ulug 2001).

1.2.2.3 OCD and gender

It is generally accepted that the overall prevalence of OCD is equal in men and women (Kolada et al. 1994; Parkin 1997), though many studies report slightly higher rates in adult women (Bebbington 1998; Fontenelle and Hasler 2008)[2]. Gender differences have been found in the average age of onset, in symptom dimensions and in patterns of comorbidity. Men and boys have repeatedly been found to exhibit an earlier age of onset (Zohar 1999; Bogetto et al. 1999; Lochner et al. 2004; Tükel et al. 2004; Karadaǧ et al. 2006; Jaisoorya et al. 2009; Ruscio et al. 2010), which results in a preponderance of males in juvenile OCD (Geller et al. 1998a; Geller 2006; Masi et al. 2010). Adult gender prevalence patterns then emerge in late adolescence (Geller 2006). Women are more likely to show an acute onset of OCD and episodic course, and onset is more likely to be related to a stressful event (Bogetto et al. 1999). Furthermore, pregnancy and the postpartum period have been identified as vulnerability periods for the onset of OCD in women (Uguz

[2]Studies examining gender and OCD generally only discuss ciswomen and cismen, people for whom the gender they were assigned at birth corresponds to the gender with which they self-identify. Studies do not include transwomen and transmen, i.e. those individuals who have a gender identity of "woman" or "man" but who were assigned "male" or "female" respectively at birth, and nor the intersex. Trans people whose gender identity lies outside of the traditional binary, most commonly for example individuals who are genderqueer or non-binary (Richards et al. 2016), or any other of the broad variety of identities in this group (Kuper et al. 2012), are also excluded. Thus epidemiological studies of OCD to date have been by their nature ciscentric (Wiktionary 2016), and we have little information on the prevalence or phenomenology of the disorder in non-cisgender populations.

and Ayhan 2011; Speisman et al. 2011) and over 60% of female OCD patients report their symptoms are worse in the week preceding menstruation (Rasmussen and Eisen 1988). Sexual, violent, and symmetry obsessions are more common in men, while contamination and checking obsessions are more common in women (Tükel et al. 2004; Labad et al. 2008; Jaisoorya et al. 2009; Torresan et al. 2009; 2013). Men exhibit higher rates of tic disorders, social phobia, PTSD and schizophrenia comorbidities while women have higher rates of comorbid eating disorders (Bogetto et al. 1999; Tükel et al. 2004; Torresan et al. 2009; 2013).

1.2.3 Clinical features

1.2.3.1 Symptomatology

The obsessions and compulsions of OCD may revolve around a variety of themes in different individuals, giving rise to a highly heterogeneous disorder across patient samples (Khanna and Channabasavanna 1988; Parkin 1997). There has been much interest in attempting to stratify the disorder into homogenous subtypes, with the recognition that research which treats OCD as a unitary construct, for example the frequent, broad comparison of mixed groups of OCD patients to healthy controls, may mask potential neurobiological, genetic, prognostic or therapeutic findings (Mataix-Cols et al. 2005; Bloch et al. 2008a).

Factor and cluster analyses are used to assess how different aspects of OCD symptomatology relate and correlate with one another. Since the early work in this field in the 1990s (Leckman et al. 1997; Summerfeldt et al. 1999), a plethora of studies have used these techniques, and have generated similar but subtly different results (Mataix-Cols et al. 2005). In a recent bid to bring together the results, Bloch et al. performed a meta-analysis where they identified the following symptom dimensions (Bloch et al. 2008a):

symmetry factor containing symmetry obsessions and ordering, repeating and counting compulsions

forbidden thoughts factor containing aggressive, sexual and religious obsessions

cleaning factor containing contamination obsessions and cleaning compulsions

hoarding factor containing hoarding obsessions and compulsions

Compulsive hoarding was previously conceptualised as a symptom dimension of OCD, but a lack of association between hoarding and OCD symptoms and a host of neurobiological, genetic and phenomenological differences between the disorders led to it being re-classified as a distinct entity in the DSM-V, under the umbrella of the obsessive-compulsive spectrum disorders category (Saxena 2007; Abramowitz et al. 2008; Mataix-Cols et al. 2010; American Psychiatric Association 2013). Thus, at present, the hoarding factor identified in the majority of work on OCD symptom dimensions would no longer be considered part of the OCD nosology.

The forbidden thoughts factor, containing aggressive, sexual and religious obsessions, has previously been termed "pure obsessional" by other authors. A criticism of this terminology is its narrow focus on observable behaviour. Mental compulsions (Abramowitz et al. 2003) and reassurance seeking[3] (Kobori et al. 2012; Kobori and Salkovskis 2013) have been found to associate with aggressive, sexual and religious obsessions, leading some authors to question the term's validity (Williams et al. 2011). Moreover, there is contention over the classification of aggressive thoughts in this category; there are proponents of an extra factor in which pathological doubts about harm and associated checking compulsions are separated from the violent impulses more phenomenologically akin to the sexual and religious obsessions in the rest of the forbidden thoughts factor (Pinto et al. 2007).

A further schema that has been proposed to classify obsessive thoughts is that of autogenous and reactive obsessions (Lee and Kwon 2003; Moulding et al. 2007b). Autogenous obsessions occur abruptly without the individual being able to identify a trigger, are of an ego-dystonic and distressing nature such as intrusive aggressive, sexual and religious thoughts, and tend to be met with attempts at thought suppression or avoidant control strategies using covert, magical or superstitious behaviours. In contrast, reactive obsessions are induced by identifiable stimuli in the environment and are more likely to be paired with physical compulsions e.g. contamination obsessions and compulsive washing behaviours.

The profile of an individual's symptomatology can include a range of symptoms from multiple symptom dimensions (Fineberg et al. 2011; Grant 2014), and tends to remain stable over time; symptoms can wax and wane within each dimension, but shifts between different dimensions or between autogenous and reactive obsessions are rare (Mataix-Cols et al. 2002b; Besiroglu et al. 2007a). Furthermore, cluster analysis has shown there may be associations between different symptom dimensions and type of comorbidity (§1.2.3.3): aggressive, sexual, religious or somatic obsessions and checking compulsions associate with anxiety disorders and depression, symmetry obsessions and counting and ordering compulsions with bipolar disorder, panic disorder and agoraphobia, contamination obsessions and cleaning compulsions with eating disorder, and autogenous obsessions with schizotypal personality features (Hasler et al. 2005; Lee and Telch 2005; Prabhu et al. 2013).

Assessment of symptom severity in OCD is approached by the use of standardised scales such as the Padua Inventory-Revised (PI-R; Sanavio 1988; Van Oppen et al. 1995; Burns et al. 1996) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al. 1989c; a; Goodman and Price 1992). The Y-BOCS is the most widely used assay, and a well-validated version of the scale has also been developed for children (Scahill et al. 1997; Storch et al. 2004; 2006, b; Yucelen et al. 2006; Gallant et al. 2008). An adaptation of the Y-BOCS, the Dimensional Yale-Brown Obsessive-Compulsive Scale, (DY-BOCS; Rosario-Campos et al. 2006) has now been developed in light of growing recognition of the dimensional nature of OCD; the original scale was thought to be too vague in some areas to map symptoms to symptom dimensions accurately (Bloch et al. 2008a). The lack of agreement between the PI-R and the Y-BOCS have led some researchers to argue that they measure different aspects of OCD phenomenology, and that both should be used to fully capture the complexity of OCD symptoms (Anholt et al. 2009).

[3] Reassurance seeking is a common compulsive behaviour in OCD that can be conceptualised as a form of checking behaviour in which patients seeks to reduce the perception of threat and responsibility with relation to a particular harm (Kobori et al. 2012; Kobori and Salkovskis 2013)

Most patients with OCD recognise that their symptoms are irrational or unreasonable, but are still unable to control their intrusive obsessions or to refrain from performing compulsions. The majority of OCD patients are thus said to have good, preserved *insight*, the lack of which can be characterised as overvalued ideation or even delusional beliefs (Neziroglu et al. 2013). Levels of insight vary between individuals however (Kozak and Foa 1994; Phillips et al. 2012; Jacob et al. 2014; Kamaradova et al. 2015), and some patients show impairments in insight, and a small proportion, around 4%, absence of insight entirely (Marazziti et al. 2002; Shavitt et al. 2010). Poor insight is associated with increased symptom severity (Catapano et al. 2001; Türksoy et al. 2002; Ravi Kishore et al. 2004; Bellino et al. 2005; Jakubovski et al. 2011 but see Shimshoni et al. 2011) and greater impairments in functioning (Matsunaga et al. 2002; Jakubovski et al. 2011), and is also linked to psychotic disorders, as the condition is more common in patients with comorbid schizophrenia (Matsunaga et al. 2002), and individuals with poor insight are more likely to have first-degree relatives with schizophrenia spectrum disorders and comorbid schizotypal personality disorders themselves (Catapano et al. 2001). In the absence of a comorbid psychotic disorder however, treatment for OCD patients with poor insight is not recommended to include anti-psychotics but to follow standard OCD protocols (O'Dwyer and Marks 2000), though poor insight still predicts poor treatment response (Erzegovesi et al. 2001; Shetti et al. 2005; Catapano et al. 2010; Demet et al. 2010; Bloch and Storch 2015).

Juvenile OCD is a serious and debilitating form of OCD occurring in children and often persisting into adulthood (Swedo et al. 1992b; March and Leonard 1996; Kalra and Swedo 2009), where it would be termed early-onset OCD (§1.2.3.2). Juvenile OCD has symptomatology which is broadly similar to that of adult OCD (Geller et al. 1998a; Stewart et al. 2007; Mataix-Cols et al. 2008; Højgaard et al. 2016), though children and adolescents have a higher prevalence of aggressive and harm-related obsessions than adults and are more likely to display reassurance seeking compulsions (Geller 2006; Mancebo et al. 2008a). Moreover, children and adolescents appear to show a greater number of different obsessions and compulsions than adults (Geller et al. 2001b). Poor insight is common in juvenile OCD patients (Storch et al. 2008; Lewin et al. 2010); children are more likely to show poor insight than older individuals (Geller et al. 2001b; Nikolajsen et al. 2011). Juvenile patients also show different patterns of comorbidity, with tic disorders being particularly common, especially in boys (Leonard et al. 1992; Ivarsson et al. 2008; Masi et al. 2010). As healthy children can be susceptible to display, usually transient, ritualised behaviour, distinguishing such behaviour from compulsions can be challenging, and the degree of distress and impairment concomitant with rituals is used as the diagnostic criterion (Evans et al. 1997; Krebs and Heyman 2015). Diagnosis is also complicated by the secrecy children often exhibit concerning their obsessions (Lewin et al. 2005). As with early-onset OCD, juvenile OCD has been conceptualised as its own developmental subtype of the disorder (Geller et al. 1998b; Eichstedt and Arnold 2001; Jaisoorya et al. 2003).

1.2.3.2 Age of onset and course

OCD is usually chronic, and worsens for many individuals at times of stress. The course of OCD can be classified as one of four types (Pinto et al. 2006):

continuous - mild variation in severity of symptoms with no remission

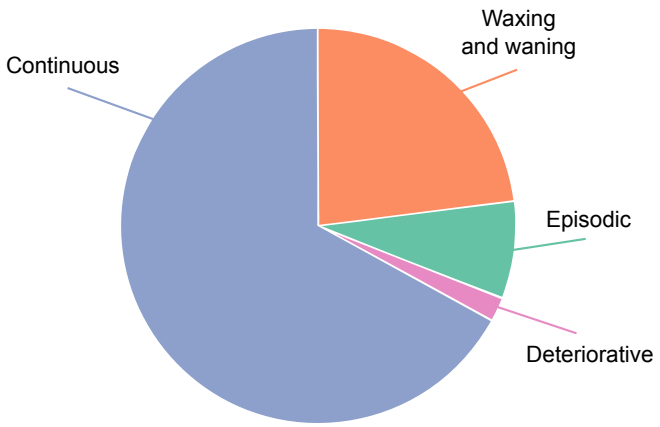

Figure 1.2.1. *Proportions of patients with the four classifications of OCD course. Data taken from Pinto et al. 2006.*

waxing and waning - periods of severe symptoms interspersed with periods of subclinical symptoms

episodic - periods of severe symptoms interspersed with periods of remission

deteriorative - symptoms continue to worsen even with treatment

The majority of patients experience the continuous form of the disorder (Figure 1.2.1; Rasmussen and Tsuang 1986; Samuels and Nestadt 1997; Pinto et al. 2006; Visser et al. 2014), and efficacious treatment often reduces or manages symptoms without achieving full remission.

Onset of symptoms is usually gradual (Pinto et al. 2006), and at least one quarter of sufferers can identify a precipitating event of some kind in the onset of their illness; such events can either be of general significance in the individual's life, such as the gain or loss of a job, or of a traumatic nature (Rasmussen and Tsuang 1986; Silva and Marks 1999; Cromer et al. 2007; Rosso et al. 2012; Dykshoorn 2014). OCD has a bimodal peak of onset, with symptoms typically beginning around the ages of 8-14 or in adulthood, in the early twenties, with the two groups termed "early-" and "late-onset" respectively (Rasmussen and Tsuang 1986; Hanna 1995). Early-onset OCD is more common in males (Fontenelle et al. 2003), and is associated with greater severity and persistence of symptoms (Skoog and Skoog 1999; Rosario-Campos et al. 2001; Fontenelle et al. 2003; Lomax et al. 2009, but see Pinto et al. 2006), greater disability (Dell'Osso et al. 2013), the presence of sexual, religious, aggression and symmetry dimensions (Grant et al. 2006b; Prabhu et al. 2013), delayed treatment seeking (Stengler et al. 2013), and different patterns of comorbidity including more tic-like compulsions and higher rates of tic disorders (Rosario-Campos et al. 2001; Millet et al. 2004; Hemmings et al. 2004; Mathis et al. 2008; Maina et al. 2008). The distinct phenomenology of early- as opposed to late-onset OCD has led to calls for patients to be stratified in terms of age of onset and considered separately (Sobin et al. 2000), and the two groups are sometimes considered different subtypes of the disorder. Evidence of differential treatment response between early- and late-onset sufferers is mixed: there are reports early-onset patients show a poorer response to SSRIs and clomipramine[4]

[4] a serotonin reuptake blocking agent of the tricyclic antidepressant class in widespread use as a therapy for OCD

(Rosario-Campos et al. 2001; Erzegovesi et al. 2001 c.f. Millet et al. 2004) but that the groups respond similarly to cognitive-behavioural therapy (CBT) (Lomax et al. 2009).

Longitudinal studies of cohorts of OCD patients, both prospective and retrospective, have provided data on the rates of persistence or remission of the disorder, both for children and adolescents and for adults. The rates of remission observed have varied widely between studies, perhaps due to methodological differences in classifying symptom severity and determining remission (especially in early studies), variable baseline symptom severity across a mixture of hospitalised patients and outpatients, and variation in levels of treatment received (Table 1.4). Even when remission was achieved relative to diagnosis of OCD, patients had often developed other psychiatric disorders, particularly in the studies of juvenile OCD (Wewetzer et al. 2001).

Several meta-analyses have attempted to bring together the disparate findings. An early study suggested that outpatients had very high rates of recovery, 60-80% experiencing partial or full remission, while less than a third of hospitalised patients showed any improvement several years later (Goodwin et al. 1969). A more recent meta-analysis found a rate of remission of 53%, though this included patients with mild and subclinical OCD according to Y-BOCS ratings (Sharma et al. 2014). A meta-analysis focussing on juvenile OCD suggested that persistence rates for this group were lower than was previously thought (March 2005), with 30-40% of juveniles maintaining full OCD into adulthood and a further 20% exhibiting subclinical OCD, while the remaining 40% achieve full remission (Stewart et al. 2004). Predictors of remission in adult and juvenile OCD were very similar, with age of onset, duration of illness and symptom severity/amount of hospitalisation common to both, and male gender additionally predicting persistence in adults (Stewart et al. 2004; Sharma et al. 2014).

1.2.3.3 Comorbidities

OCD has been found to present comorbidly with a range of other psychiatric illnesses including mood disorders of unipolar and bipolar depression, anxiety disorders such as generalised anxiety disorder and social phobia, psychotic disorders such as schizophrenia, personality disorders, disruptive behaviour disorders such as attention-deficit/hyperactivity disorder (ADHD), and other obsessive-compulsive spectrum disorders such as hoarding (previously considered a subtype of OCD and now its own disorder), trichotillomania, skin picking disorder and body dysmorphic disorder (Pigott et al. 1994). It is so frequently comorbid with other disorders that patients who suffer from OCD alone are in the minority (Pallanti et al. 2011; Torres et al. 2006b; Denys et al. 2004b) and overall estimates of comorbidity reach up to 92% (LaSalle et al. 2004). As well as contributing to the individual burden per patient, and often hindering the diagnosis of OCD with a complex multiple disorder presentation, comorbidities can interact with the phenomenology of OCD and there are strong associations between certain disorders and symptom dimensions or course of the illness (Hasler et al. 2005; Mathis et al. 2013; Torres et al. 2016a), to the degree where some researchers have attempted to classify subtypes of OCD based upon their comorbidities (Nestadt et al. 2003; 2009).

Unipolar depression is the illness most frequently comorbid with OCD, with estimates that around a third of OCD patients are depressed at any one time (Ricciardi and McNally 1995; Perugi et al. 1997; Overbeek

Table 1.4. *Rates of remission found in prospective follow-up studies of OCD in juveniles and adults*

Study	Location	Sample size	Age at study onset (years)*	Follow-up duration (years)	Partial remission rate (%)	Full remission rate (%)
Juveniles						
Flament et al. 1990	US	25	6-18	4.4 ± 1.7	-	32
Leonard et al. 1993	US	54	14.0 ± 3.0	3.4 ± 1.0	46	11
Thomsen 1994	Denmark	47	8-17	6-22	25.5	27.7
Wewetzer et al. 2001†	Germany	55	14.6	11.2 ± 3.7	27.3	29.1
Micali et al. 2010	UK	142	13.5 ± 2.6	5.1 ± 2.7	0.7	54.8
Becker Nissen et al. 2014	Denmark	95	13.9 ± 3.4	7	13.7	46
Adults						
Eisen et al. 1999	US	66		2	47	12
Skoog and Skoog 1999	Sweden	144	36.0 ± 8.2	47	28	20
Steketee et al. 1999	US	100	35	1 5	15 22	27 53
Reddy et al. 2005†	India	75	30.1 ± 9.5	11-13	25	40
Van Oppen et al. 2005†	Netherlands	102	36.2 ± 10.7	5		53.5
Math et al. 2007†	India	77	22.9 ± 9.66	5-6		72
Catapano et al. 2006	Italy	79	31.5 ± 10.3	3	27	38
Eisen et al. 2010 Eisen et al. 2013†	US	214 213	39.8 ± 12.8	2 5	16.8 22.1	5.6 16.9
Braga et al. 2010	Brazil	42	36.8 ± 13.2	2	47.6	31.0
Marcks et al. 2011	US	113	35.21 ± 11.95	1 5 10 15	-	16 25 31 42
Bloch et al. 2013†	US	83	42.0 ± 9.9	1	31	20
Cherian et al. 2014b	India	94	27.6 ± 8.5	1		58
Cherian et al. 2014a	India	106	28.05 ± 9.06	5	28	65

* Mean (with standard error if possible) given if available, range if mean was not quoted.
† Study was retrospective as opposed to prospective.
Remission rates relate to a diagnosis of OCD only, and ignore the presence of any other psychiatric disorders.
Statistics not provided for partial remission rates in some studies.

et al. 2002; Denys et al. 2004b; Anagnostopoulos et al. 2016) (but see Milanfranchi et al. 1995 for lower estimates), and that 50-80% of OCD patients experience depressive episodes at some point during their lifetime (Rasmussen and Tsuang 1986; Crino and Andrews 1996; Brown et al. 2001; Nestadt et al. 2001; Pinto et al. 2006; Quarantini et al. 2011). Depression is ten times more prevalent in OCD patients than in the general population (Denys et al. 2004b), though there is evidence that the symptom profile of OCD-comorbid depression may differ from that of pure unipolar depression (Fineberg et al. 2005). Comorbid depression also occurs in child and adolescent OCD sufferers (Geller et al. 1996; Anagnostopoulos et al. 2016) and is associated with increased symptom severity (Canavera et al. 2010; Peris et al. 2010; Brown et al. 2015), but is thought to occur at lower rates with the risk of depression increasing with age (Geller 2006; Peris et al. 2010). Patients often identify a causal link between their OCD symptoms and their depression; depression predates OCD onset very infrequently (Ricciardi and McNally 1995), and around three quarters report that social or occupational impairment as a direct result of OCD symptoms induced their depression (Rasmussen and Tsuang 1986). OCD-depression patients also tend to have a more chronic and severe course of OCD, with an earlier onset and longer duration of illness, reduced quality of life and functioning, and increased hospitalisation and a higher number of suicide attempts (Perugi et al. 1997; Masellis et al. 2003; Hong et al. 2004; Tükel et al. 2006b; Besiroglu et al. 2007b; Abramowitz et al. 2007). Support for the presence of comorbid depression as a predictor of treatment response has been mixed (Keeley et al. 2008), though it has been hypothesised that *severe* as opposed to milder depression does predict response to psychotherapy (Abramowitz and Foa 2000; Abramowitz 2004), but it is noteworthy that the majority of comorbid OCD-depression patients report their depressive symptoms as the reason they seek treatment (Zimmerman and Mattia 2000).

Similarly, bipolar disorder (BD) is highly co-morbid with OCD (Angst et al. 2005b; Amerio et al. 2014; Peng and Jiang 2015), particularly in adolescents (Amerio et al. 2015; Tonna et al. 2015), and it has been suggested the two disorders may be etiologically related (Cederlöf et al. 2015); estimates range from 4-35% for OCD prevalence in BD (Chen and Dilsaver 1995; Krüger et al. 1995; Altindag et al. 2006; Koyuncu et al. 2010; Dell'Osso et al. 2011) and between 10-20% for BD in OCD (Perugi et al. 1997; 2002). OCD-bipolar patients show different profiles of symptom dimensions (higher rates of sexual obsessions and lower rate of ordering compulsions (Perugi et al. 1997; 2002)), and report greater functional impairment with smaller average improvements after treatment than pure OCD patients (Perugi et al. 2002; Boylan et al. 2004; Joshi et al. 2010).

Schizophrenia is another disorder which has been linked to OCD; schizophrenia is eight times more prevalent in OCD patients than in the general population (Denys et al. 2004b). Most research on the comorbidity between schizophrenia and OCD has examined the increased prevalence of OCD or obsessive-compulsive symptoms in schizophrenic populations, with recent meta-analyses giving figures of 23% and 12.1% (Buckley et al. 2009b; Achim et al. 2011). The diagnosis of OCD is associated with an 3.5-fold increased risk of an individual developing schizophrenia (Tien and Eaton 1992; Meier et al. 2014). So prevalent is OCD in conjunction with schizophrenia that is has been proposed that it be classified as its own psychiatric disorder subtype - *schizo-obsessive disorder* (Zohar 1997; Rajkumar et al. 2008; Poyurovsky 2012), and various studies have found that patients suffering from it have a particularly high disease burden, poor response to treatment and poor general prognosis (Berman et al. 1995; Cunill et al. 2009; De

Haan et al. 2013; Zhou et al. 2016). Others however have argued that comorbid OCD and schizophrenia does not comprise a distinct clinical entity (Frías et al. 2014a; b).

Disruptive behaviour disorders have also been linked to OCD in juvenile sufferers. 51% of children and 36% of adolescents with OCD also have ADHD, and 51% of children and 47% of adolescents have oppositional defiant disorder, though neither is common in adults (Geller 2006). ADHD phenomenology is unchanged in OCD patients relative to those without the disorder, and it is more prevalent in boys (Geller 2006). Recent work has disputed the link between ADHD and OCD, instead postulating that OCD is commonly mistaken for ADHD in children, to the detriment of their treatment (Abramovitch 2016).

Both small clinical studies and analysis of large community samples have shown a high prevalence of personality disorders in OCD (Mavissakalian et al. 1990; Rodrigues Torres and Del Porto 1995; Skodol et al. 1995; Matsunaga et al. 1998; Torres et al. 2006a; Friborg et al. 2013); in the community 74% of OCD patients screened positive for personality disorders and 53% met the criteria for multiple categories of personality disorder (Torres et al. 2006a). The cluster C categories of personality disorders, anxious, avoidant and obsessive-compulsive, are held to be the group most common in OCD (Matsunaga et al. 1998; Torres et al. 2006a). In particular, the relationship between obsessive-compulsive personality disorder (OCPD) and OCD is widely studied (Du Toit et al. 2001; Eisen et al. 2006a; Gordon et al. 2013; Starcevic et al. 2013) but remains controversial. It has been argued that OCPD is often not the personality disorder found to have the highest prevalence in OCD populations, and does not bear a special relation to OCD, despite its name (Baer and Jenike 1992; Wu et al. 2006), whilst others have stated that the OCD with comorbid OCPD may constitute its own subtype of OCD (Coles et al. 2008; Garyfallos et al. 2010). The cluster A categories, particularly paranoid, schizoid and schizotypal personality disorders, are also highly comorbid in OCD (Torres et al. 2006a; Matsunaga et al. 1998) and predict poorer treatment response (Baer and Jenike 1992; Black and Noyes, Jr. 2009). OCD patients with OCPD or avoidant personality disorder were recently found to be more likely to experience a new episode of OCD, and those with borderline personality disorder were more likely to suffer a relapse if they achieved remission (Ansell et al. 2011).

The prevalence of the obsessive-compulsive spectrum disorders, a category which includes body dysmorphic disorder, tic disorders including Tourette's syndrome, trichotillomania, skin picking and hypochondriasis, is also elevated in the OCD population relative to controls (Phillips et al. 2010; Lochner et al. 2014), and it has been suggested they are most common in early-onset OCD (Stewart et al. 2005; Mathis et al. 2008; Janowitz et al. 2009). The high comorbidity is perhaps unsurprising, as the move to create an obsessive-compulsive spectrum grouping in DSM-V was prompted by considerable phenomenological overlap between each of the disorders and OCD (Barsky 1992; Swedo and Leonard 1992; Steingard and Dillon-Stout 1992), as well as similarities in terms of familial and genetic features, neurocircuitry and treatment response, factors which suggest they may share a common etiology (Hollander et al. 2009). The comorbidity of body dysmorphic disorder, an illness characterised by a distressing preoccupation with an imagined defect in appearance (Frare et al. 2004), has been particularly well studied; lifetime prevalence is around 12% among OCD sufferers and is associated with poorer insight of patients into their obsessions and compulsions (Simeon et al. 1995; Conceição Costa et al. 2012). Finally, tic disorders are highly prevalent in OCD, particularly in children where 40% of patients exhibit tics (Kostek et al. 2016), and the

presence of comorbid tics has been proposed as a separate subtype of OCD (Leckman et al. 2010). Tics are most common among males and those with a lower age at onset, and are associated with poor treatment response (Geller 2006; Ginsburg et al. 2008; Bloch and Storch 2015; Kostek et al. 2016).

1.2.3.4 Quality of life

OCD is a disabling and debilitating disorder which has profound impact on the quality of life (QoL) of sufferers, both in adults and in children and adolescents (Koran 2000; Srivastava and Bhatia 2008; Lack et al. 2009; Subramaniam et al. 2013; Macy et al. 2013). Reductions in QoL have been reported across all spheres of functioning, including in social functioning, mental, physical and general health, work and school performance, leisure, domestic functioning, and vitality and emotional wellbeing (Piacentini et al. 2003; 2007).

OCD symptom severity is frequently found to modulate reduced quality of life (Eisen et al. 2006b; Rodriguez-Salgado et al. 2006; Weidle et al. 2014; Storch et al. 2014), with some reports specifying obsession rather than compulsion severity to be the important factor (Masellis et al. 2003; Chaudhury et al. 2006; Hou et al. 2010). Furthermore, the presence of comorbidities (Huppert et al. 2009; Weidle et al. 2014), in particular depression (Masellis et al. 2003; Stengler-Wenzke et al. 2007; Cassin et al. 2009; Hauschildt et al. 2010; Hou et al. 2010; Jacoby et al. 2014; Storch et al. 2014), is associated with lower QoL; symptom severity of depression has been found to correlate with reduced QoL (Moritz et al. 2005; Rodriguez-Salgado et al. 2006; Lee et al. 2014). Compared to other patient groups, OCD patients have a similar QoL to schizophrenics, but better than that of those with depression and heroin addicts (Bobes et al. 2001; Bystritsky et al. 2001; Solanki et al. 2010; Negm et al. 2014 but see Srivastava et al. 2011). QoL has been found to improve with a range of treatments, including hospitalisation programs (Bystritsky et al. 1999; 2001; Hertenstein et al. 2013), SSRIs (Tenney et al. 2003) and CBT (Moritz et al. 2005; Diefenbach et al. 2007; Norberg et al. 2008), but often fails to reach the QoL levels of healthy controls (Bystritsky et al. 1999; 2001; Huppert et al. 2009; Hertenstein et al. 2013).

The area of greatest disability in OCD is consistently demonstrated to be that of social functioning (Grabe et al. 2000; Bobes et al. 2001) and the degree of impairment has been shown to correlate with symptom severity (Koran et al. 1996a; Rosa et al. 2012; Kugler et al. 2013). Patients report difficulties in family relationships and having fewer friends or difficulty in maintaining their friendships (Hollander et al. 1996; Barrett et al. 2000). A range of factors have been identified which may predict impaired social functioning including the presence of sexual/religious obsessions and comorbidities of hoarding, unipolar depression (Eisen et al. 2006b; Albert et al. 2010b), PTSD and eating disorders (Rosa et al. 2012). Children with OCD are also likely to be impaired socially, regardless of any ADHD comorbidity (Kim et al. 2012). Moreover, following treatment OCD patients generally experience improvements in most measures of QoL, but a recent study found social QoL to be the only domain that remained unchanged (Hertenstein et al. 2013). Lowered self-esteem is also highly prevalent and is reported by 92% of patients, as is sexual dysfunction (Van Minnen and Kampman 2000; Vulink et al. 2006; Kendurkar and Kaur 2008; Thakurta et al. 2014), and difficulties with school or work attendance or performance (Grabe et al. 2000; Sørensen et al. 2004); ~40% of patients have been prevented from working entirely, with an average loss of time in employment of

two years (Hollander et al. 1996; Mancebo et al. 2008b). Physical health is an area that may be less affected however; OCD patients have similarly low QoL to that of schizophrenics in all areas, except physical health, where they are less impaired (Bobes et al. 2001; Gururaj et al. 2008), and some studies have found their physical health is similar to the general population (Koran et al. 1996a).

OCD patients have a much higher rate of suicidality and suicidal ideation than those in the general population (Alonso et al. 2010), and the degree of suicidal ideation has been shown to positively correlate with symptom severity (Dhyani et al. 2013). Rates of lifetime suicidal ideation range from 46-62% (Sørensen et al. 2004; Kamath et al. 2007; Torres et al. 2007b) and suicide attempts from 10-27% of individuals surveyed (Sørensen et al. 2004; Kamath et al. 2007; Torres et al. 2007b), and over half of patients had suicidal ideation at the point of investigation (Balci and Sevincok 2010). The risk of mortality for OCD patients is elevated overall, for both natural and unnatural causes (Meier et al. 2016).

The impact of OCD on quality of life is not simply restricted to that of the patient themselves, but also affects the members of their families (Black et al. 1998; Thomas et al. 2004; Stengler-Wenzke et al. 2004b; Gururaj et al. 2008; Grover and Dutt 2011), with comparable levels of burden induced to that of schizophrenia (Kalra et al. 2009; Jayakumar et al. 2002). Relatives of individuals with OCD report reduced quality of life when surveyed (Stengler-Wenzke et al. 2006; Albert et al. 2007; Cicek et al. 2013), and experience feelings of distress, guilt and depression as well as financial problems and significant social impairment (Cooper 1996; Magliano et al. 1996; Steketee 1997; Amir et al. 2000; Geffken et al. 2006; Murphy and Flessner 2015).

Another interaction between an individual's relatives and their OCD is the common issue of family accommodation, defined as the ways in which family members take part in the performance of rituals, avoidance of anxiety-provoking situations or modification of daily routines to assist their relative suffering from OCD (Lebowitz et al. 2012). Family accommodation is widespread (Calvocoressi et al. 1995; Albert et al. 2010a; Gomes et al. 2014; Cosentino et al. 2015) and correlates with symptom severity (Calvocoressi et al. 1999; Bipeta et al. 2013; Gomes et al. 2014; Strauss et al. 2015; Wu et al. 2016), being particularly common around patients with contamination obsessions and cleaning compulsions (Stewart et al. 2008; Albert et al. 2010a), and more likely performed by relatives sensitive to feelings of guilt (Cosentino et al. 2015) and with a history of anxiety disorders themselves (Albert et al. 2010a). It is associated with family dysfunction and stress (Calvocoressi et al. 1995), though it is likely performed with the aim of reducing patient distress (Calvocoressi et al. 1995; Waters and Barrett 2000). Furthermore, family accommodation and family dysfunction are associated with poorer prognosis, especially if present post-treatment (Amir et al. 2000; Barrett et al. 2005; Ferrão et al. 2006; Merlo et al. 2009; Peris et al. 2012; Boeding et al. 2013; Morgan et al. 2013; Cherian et al. 2014b).

1.2.3.5 Treatment

Treatments for OCD have undergone major advances in the past few decades. Psychotherapy, in the form of Cognitive-Behavioural Therapy (CBT), often with Exposure and Response Prevention (ERP), is widely acknowledged to be efficacious (Rosa-Alcázar et al. 2008; Ponniah et al. 2013; McKay et al. 2015; Öst et

al. 2016), as is pharmacotherapy with clomipramine or selective-serotonin reuptake inhibitors (SSRIs) as firstline medications (Fineberg and Gale 2005; Fineberg et al. 2012; 2013), with potential augmentation by antipsychotics (Bloch et al. 2006). Therapeutic outcomes are optimised when treatment plans are tailored to the individual, based upon their own preferences and needs (Patel and Simpson 2010).

In ERP, patients are subjected to the situations or stimuli they find frightening, via their physical presence or imagination (Foa et al. 1980; 1985), and asked to focus specifically on their anxiogenic aspects, but to refrain from performing their compulsions and wait for the fear response to decline. Repeated exposure over time allows the patients to learn that their anxiety will subside naturally, without the need for compulsions (Foa 2010; Grant 2014). ERP was first developed by Meyer 1966, and in its traditional form is conducted in regular sessions between patient and therapist, with the patient "topping up" the therapy alone between sessions (Foa 2010), but effective versions have been developed that are administered by telephone (Lovell et al. 2006; Turner et al. 2009; 2014), computer (Greist et al. 2002; Andersson et al. 2012), or by the patient themselves (Abramowitz 1996; Mataix-Cols and Marks 2006; Van Oppen et al. 2010). Numerous studies have confirmed the efficacy of ERP (Rachman et al. 1971; Lindsay et al. 1997; Franklin et al. 2000; Valderhaug et al. 2007; Simpson et al. 2008); outcomes are significantly better when ERP is given alongside drug therapy than if drugs are given alone (Kampman et al. 2002; Simpson et al. 2004; Foa et al. 2005; Romanelli et al. 2014). However, ERP can be distressing for patients and hence 25-30% of patients discontinue treatment prematurely (Abramowitz 2006), markedly reducing its efficacy (Simpson et al. 2011a).

CBT in OCD aims to isolate and correct dysfunctional beliefs held by patients. It is based on the rationale that whilst most people in the wider population experience intrusive, unwanted thoughts (Rachman and Silva 1978; Salkovskis and Harrison 1984; Clark 1992), the faulty interpretation of the thoughts by the attachment of exaggerated significance and feelings of responsibility in OCD causes distress and ultimately induces compulsions (Salkovskis 1985; 1989; Rachman 1997; 1998), a theory which is supported by findings in non-clinical populations (Freeston et al. 1991; 1992; Purdon and Clark 1993; 1994). Once the intrusive thoughts are identified, patients work with their therapists to recognise the ways in which they are distorted from rationality and to change their interpretation (Grant 2014). Modified techniques have been developed to extend the therapy to treat juvenile cases as well as those of adults (Piacentini and Langley 2004; Martin and Thienemann 2005). CBT and ERP have been directly compared in head to head trials and found to be of similar efficacy (Whittal et al. 2005 but see Fisher and Wells 2005), though rates of uptake and adherence to CBT may be even lower than those for ERP therapy (Mancebo et al. 2011). The two techniques are complementary however, and are frequently and effectively used in combination in psychotherapy (Cordioli 2008; Franklin et al. 2015).

Clomipramine was first trialled in OCD in the 1960s, and was found to be more effective than other tricyclic antidepressants (Pizarro et al. 2014). Since then a plethora of studies have testified to its efficacy (Thorén et al. 1980b; Flament et al. 1985; The Clomipramine Collaborative Study Group 1991; DeVeaugh-Geiss et al. 1989; Montgomery et al. 2001), which appears to be similar to that of SSRIs in head to head studies (Freeman et al. 1994; Piccinelli et al. 1995; López-Ibor et al. 1996; Zohar et al. 1996; Koran et al. 1996b; Bisserbe et al. 1997; Mundo et al. 2000) but with a higher incidence of adverse effects (Flament and Bisserbe 1997; Pigott and Seay 1999; Mundo et al. 2001; Decloedt and Stein 2010; 2012).

As a consequence there is a lower adherence rate for clomipramine versus SSRI therapy (Choi 2009). Thus SSRIs are recommended as the firstline treatment over clomipramine (Fineberg et al. 1992; Fineberg and Gale 2005; Antai-Otong 2007; Grant 2014), often in conjunction with psychotherapy (Greist et al. 2003; Skapinakis et al. 2016). Clinical trials consistently prove the efficacy of a range of SSRIs (Greist et al. 1995a; Soomro et al. 2008; Decloedt and Stein 2012), including fluvoxamine (Price et al. 1987; Perse et al. 1987; Goodman et al. 1989b; Goodman et al. 1996; Jenike et al. 1990b), fluoxetine (Montgomery et al. 1993; Geller et al. 2001a; Liebowitz et al. 2002), sertraline (Jenike et al. 1990a; Greist et al. 1995b; Kronig et al. 1999), paroxetine (Hollander et al. 2003; Kamijima et al. 2004; Geller et al. 2004), citalopram (Koponen et al. 1997; Thomsen et al. 2001; Mukaddes et al. 2003) and escitalopram (Stein et al. 2007b), with individual SSRIs showing comparable efficacy to each other (Soomro et al. 2008; Issaria et al. 2016). The optimal doses of SSRIs have been found to be higher than those used in depression, and such usage gives a concomitantly greater risk of side effects, which can be a cause of treatment discontinuation by patients (Bloch et al. 2010; Decloedt and Stein 2010). Furthermore, it is widely held that SSRIs take longer to achieve their effects in OCD than in depression (Grant 2014), but recent evidence contradicts this (Issaria et al. 2016; Varigonda et al. 2016). If patients do not improve with typical SSRI or clomipramine monotherapy, the administration of the drugs may be modified by either the intravenous administration of clomipramine (Fallon et al. 1998), intra-SSRI and SSRI-clomipramine switching (Denys et al. 2004a; Bhui 2004) or combination therapy of clomipramine in conjunction with an SSRI (Marazziti et al. 2008).

In the event that patients have not improved sufficiently with the firstline medications there are a range of further treatments that can be used (Castle et al. 2015). Augmentation of firstline OCD therapies with atypical antipsychotics is common but has mixed evidentiary support (Sareen et al. 2004), though it has been suggested that it may be efficacious in up to a third of treatment-refractory patients (Bloch et al. 2006). In a randomized clinical trial which compared an antipsychotic against ERP augmentation of SSRI therapy the antipsychotic did not differ significantly from placebo (Simpson et al. 2013), though this disagrees with meta-analyses based upon smaller studies (Dold et al. 2013; Veale et al. 2014). Tolerability issues due to the substantial adverse effect profile of atypical antipsychotics remain a barrier to their therapeutic utilisation (Haddad and Sharma 2007). Other more radical treatments for refractory patients include transcranial magnetic stimulation (TMS; Blom et al. 2011; Nauczyciel et al. 2014), gamma ventral capsulotomy (Lopes et al. 2014) and deep brain stimulation (DBS) of a range of anatomical targets (Blomstedt et al. 2013; Sedrak et al. 2013; Kisely et al. 2014; Alonso et al. 2015a), though the use of these therapies is currently limited and research is ongoing.

Despite the availability of the aforementioned therapies, treatment nonresponse is still a common problem in OCD (Pallanti et al. 2002; 2004; Pallanti and Quercioli 2006), with 40-60% of patients treated with SSRIs not achieving a satisfactory response (Kellner 2010). Predictors of treatment non-response have been the subject of much research, and greater duration of illness is the factor that has been identified most consistently (Goodwin et al. 1969; Alarcon et al. 1993; Storch et al. 2006a; Jakubovski et al. 2013 but see Ginsburg et al. 2008). In addition to the impact of poor insight, family dysfunction and the comorbidities of depression and tic disorders as have been previously described (§1.2.3.1, 1.2.3.4 and 1.2.3.3 respectively), other factors include greater baseline symptom severity Goodwin et al. 1969; Alarcon et al. 1993; Mataix-Cols et al. 1999a; Mataix-Cols et al. 2002a; Tükel et al. 2006a; Storch et al. 2006a; Kim et al.

2011; Morgan et al. 2013; Knopp et al. 2013; Kyrios et al. 2015), earlier age of onset (Shetti et al. 2005; Jakubovski et al. 2013), greater disability (Tükel et al. 2006a) and older age (Storch et al. 2006a). Patients with comorbid post-traumatic stress disorder may respond better to treatment than those with OCD alone (Shavitt et al. 2010). Attempts to link specific symptom dimensions to treatment response have been conflicting (Mataix-Cols et al. 1999a; Kellner 2010; Stein et al. 2007a), but potential associations include the presence of cleaning rituals (Alarcon et al. 1993; Shetti et al. 2005) and sexual obsessions (Mataix-Cols et al. 2002a; Shetti et al. 2005, but see Stein et al. 2007a); hoarding was also associated with poor response prior to it being considered a separate disorder (Mataix-Cols et al. 1999a; Rufer et al. 2006; Stein et al. 2007a).

Psychiatric disorders are often identified as one of the sources of greatest unmet need in healthcare (Bebbington 2000) and figures suggest that OCD is no exception. Criticism has been levelled that the calculation of unmet need in a population is based on prevalence estimates which do not always take clinical significance measures into account, and so it has been hypothesised that the detection of subclinical disorders in such studies inflates estimates of unmet need (WHO World Mental Health Survey Consortium 2004). The general findings of the WHO however, pointed towards persistent unmet need through the disproportionate allocation of resources; a plethora of subclinical cases were treated while large numbers of the most severely afflicted cases were not (WHO World Mental Health Survey Consortium 2004). This, combined with data which suggests that OCD is not one of the disorders for which prevalence estimates change radically when clinical significance is focussed upon (Narrow et al. 2002), means that we can safely accept the estimates of unmet need, and thus illness burden, in OCD to be real.

Effectively meeting the need of individuals with OCD for treatment requires high levels of two related concepts: treatment seeking and treatment adequacy. Treatment seeking describes how likely sufferers are to pursue treatment for their condition and treatment adequacy is the degree to which the treatments thought to be most effective according to the latest clinical guidelines are provided for patients, and how quickly accurate diagnosis and delivery of such treatments occurs. In a large sample of 1.7 million people registered with a healthcare provider in California, the one year prevalence of clinically recognised OCD was only 0.084%, much lower than most community prevalence estimates (§1.2.2.1), which suggests many OCD sufferers are experiencing unmet need, either through insufficient recognition of the disorder, and thus treatment inadequacy, or insufficient treatment seeking (Fireman et al. 2001).

In general, levels of treatment seeking in OCD tend to be very low (Mayerovitch et al. 2003; Subramaniam et al. 2012; Schwartz et al. 2013; Mack et al. 2014), with a large proportion of patients recognising the irrationality of their symptoms (insight is generally preserved) but still finding it difficult to get help; in some cases sufferers work to attempt to conceal symptoms even from their families (Torres and Prince 2004). OCD has been shown to have the longest latency to treatment of any of the mood or anxiety disorders (Altamura et al. 2010); a recent study showed patients first acknowledged their symptoms to family members after an average of seven years and received a diagnosis and treatment after an average of 13 years (Sørensen et al. 2004). Embarrassment, fear of hospitalisation or arrest, and fear of judgment or social stigma may all contribute to the barrier to treatment seeking, with sufferers more likely to disclose obsessions and compulsions seen as more "acceptable" (e.g. checking behaviours) than "unacceptable" (e.g. violent obsessions) (Simonds and Elliott 2001; Simonds and Thorpe 2003; Torres and Prince 2004;

Beşiroğlu and Ağargün 2006; Belloch et al. 2009; Marques et al. 2010; Cathey and Wetterneck 2013; Glazier et al. 2015a; Vuong et al. 2016). Patients also report concerns about the potential cost of treatment, as well as a lack of knowledge of available treatment options (Marques et al. 2010; Mancebo et al. 2011; Gentle et al. 2014). When patients do present to medical professionals for treatment, it is often regarding the physical or mental sequelae of the disorder rather than a wish to treat the disorder itself, for example visiting a dermatologist concerning raw, chapped hands after excessive washing (Heyman et al. 2006). Clinically, poorer insight (Beşiroğlu et al. 2004; Demet et al. 2010; García-Soriano et al. 2014) decreases the likelihood of treatment-seeking while the presence of violent or religious obsessions (Mayerovitch et al. 2003; Beşiroğlu et al. 2004) or co-morbidities increases the likelihood of treatment seeking (Goodwin et al. 2002; Beşiroğlu et al. 2004). Several demographic features also interact with treatment seeking; people who are younger, from a lower income level, who are unmarried, and those from ethnic minorities within their countries are also less likely to seek treatment (Goodwin et al. 2002; Neighbors et al. 2007; 2008; Demet et al. 2010; Fernández de la Cruz et al. 2015; 2016). However, the increasing frequency of OCD diagnoses may give hope that the increased visibility of the condition in the media and knowledge of the disorder in the psychiatric community is encouraging individuals to come forward for treatment (Stoll et al. 1992).

Treatment adequacy for OCD may also be very poor; around a third of OCD patients in treatment in the US received pharmacotherapy at appropriate doses, and less than 10% psychotherapy (Blanco et al. 2006; Torres et al. 2007a), while half of patients in the UK report their treatment to be inadequate (Vuong et al. 2016). Few studies have carried out detailed assessments of treatment adequacy in patient samples, and in those broad studies which exist, few have analysed OCD-specific data. However, recent surveys have suggested that only 40-50% of OCD patients receive treatment judged to be minimally adequate (Denys et al. 2002; Stobie et al. 2007; Kasteenpohja et al. 2016), a figure which closely matches the proportion of children referred to a British OCD clinic without having received appropriate treatment (Chowdhury et al. 2004). Lack of recognition of OCD by doctors may mediate treatment inadequacy, as 94% and 70% of patients of two dermatology and psychiatry clinics respectively who screened positive for OCD symptoms were not assessed for the disorder by their clinicians (Fineberg et al. 2003; Wahl et al. 2010), and a recent survey of general physicians using hypothetical scenarios found a misdiagnosis rate of over 50% (Glazier et al. 2015b). Additionally even psychiatrists may have insufficient expertise; child psychiatrists in Norway reported inexperience and a lack of training in the treatment of OCD (Valderhaug et al. 2004). In particular there is thought to be a shortage of qualified therapists to administer CBT (Shapiro et al. 2003; Cavanagh 2014). Additionally, wealth may form a barrier to receiving specialist treatment; in Nigeria, a less economically developed country, estimates of unmet need for anxiety disorders (including OCD) are particularly low compared to reports from elsewhere (Gureje and Lasebikan 2006) and in the US the likelihood of receiving specialist psychiatric treatment negatively correlated with income (Alegría et al. 2000). Finally, OCD patient satisfaction with treatment is mixed, and negatively correlates with symptom severity (Mavrogiorgou et al. 2013).

1.2.4 Summary

OCD is a chronic, debilitating neuropsychiatric disorder characterised by obsessions and compulsions. Whilst prevalence estimates have varied across studies, it is generally thought to affect 1-3% of the population worldwide, and its sufferers include children and adults from all socio-cultural backgrounds. It is increasingly recognised that OCD is not a unitary disorder, and that the thematic content of obsessions and compulsions can vary greatly between patients. Consequently, a great deal of research has focussed upon delineating the broad spectrum of symptoms into categories, known as symptom dimensions. OCD displays a high degree of comorbidity with other psychiatric disorders, a factor which only adds to its impact on the quality of life of patients and their families. The disorder is poorly treated; a substantial proportion of patients show no improvement and are considered refractory to treatment, and in those patients for whom therapy is efficacious full remission of the disorder is frequently not achieved.

With the discovery in the 1980s and 90s that OCD was much more common in the population than previously thought came a rise in the number of studies attempting to clarify its neuropsychological basis (Boschen 2008). Our knowledge of the neuropathology of OCD is now increasingly well understood, though lamentably such progress has not yet translated into significant treatment advances; there have been no novel treatments developed for OCD in recent years (Pallanti et al. 2014). The continued search for an ever more precise understanding of the neurobiological underpinnings of OCD reflects a recognition within the neuroscience community of the great individual and societal burden of the disorder and the need to improve its treatment outlook. Such strong neurobiological interest in OCD builds upon a now extensive body of research but shows no sign of abating, as is described in the next section.

1.3 Neuroanatomical substrates of OCD

The neural basis of OCD has been the subject of intensive research for almost three decades. The prevailing neurobiological theory is that of aberrant fronto-striatal circuitry. Cortical regions and specific areas of the striatum are linked by projections from the cortex to the striatum, the striatum to the thalamus via the globus pallidus and the thalamus back to the cortex again to form cortico-striato-thalamo-cortical (CSTC) loops which are partly segregated and organised in parallel (Alexander et al. 1986; Alexander and Crutcher 1990). There exist multiple CSTC loops which are thought to be involved in different neurocognitive domains. Regions in a loop comprising projections between the lateral OFC, head of the caudate and ventral striatum, and the mediodorsal thalamus via the internal pallidus, known as the affective or limbic loop (Haber 2003), are thought to be sites of dysfunction that result in OCD pathology (Hoehn-Saric 1997; Hoehn-Saric and Greenberg 1997; Menzies et al. 2008). Modelling of the limbic loop has been extended to also incorporate the hippocampus, anterior cingulate (ACC) and basolateral amygdala (Menzies et al. 2008).

Evidence to support the involvement of the limbic CSTC loop, in particular the OFC and the caudate, has converged from studies using a variety of neuroimaging techniques including positron emission tomography (PET), single-photon emission computed tomography (SPECT), structural magnetic resonance

imaging (MRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI). The general consensus is that these structures are hyperactive relative to healthy controls at rest, with activity increasing upon provocation of symptoms and decreasing with successful treatment, and are also the site of grey and white matter abnormalities.

1.3.1 Neuroimaging findings

1.3.1.1 Resting-state

Whilst findings from individual resting-state PET and SPECT studies have been mixed (Table A.1), a meta-analysis of PET and SPECT imaging demonstrated hyperactivity in OFC and the caudate to be the most consistent findings (Whiteside et al. 2004), despite an earlier meta-analysis focussed on the caudate giving negative results (Aylward et al. 1996). These findings were supported by a recent fMRI study, in which increased amplitude of low-frequency fluctuations was found in OCD patients in the OFC and ACC among other areas (Hou et al. 2012).

A plethora of MRS studies have also been performed on OCD patients in the resting state in order to evaluate levels of common metabolites; a recent meta-analysis found that levels of N-acetylaspartate (NAA) are reduced in the frontal cortex[5], specifically in the medial PFC (mPFC), of OCD patients, and that the reduction correlates with symptom severity (Aoki et al. 2012). Other findings that receive support from the somewhat inconsistent literature in the field (Naaijen et al. 2015) are reduced NAA in the ACC and caudate, reduced glutamate/glutamine in the ACC, increased glutamate/glutamine in the caudate and increased choline-containing compounds (Cho)[6] in the thalamus, parietal white matter and hippocampus (Brennan et al. 2012).

1.3.1.2 Symptom provocation

With the advent of fMRI technology, many more studies of symptom provocation and treatment were conducted using fMRI in preference to PET. Results from studies conducted under symptom provocation have been more consistent with respect to evidence of OFC involvement in OCD pathophysiology. The results of individual symptom provocation studies are reported in Table A.2. Meta-analyses of the body of work have strongly supported the increased activation of OFC and cingulate regions during symptom provocation, but results with regard to the caudate are more mixed (Menzies et al. 2008; Rotge et al. 2008).

1.3.1.3 Treatment-induced changes and treatment predictors

Two major approaches have been used to investigate the neural basis of treatment of OCD. In *treatment mechanism* studies, patients are scanned before and after a specified course of treatment and the two scans

[5] NAA is held to be a marker of neuronal integrity, and low levels are interpreted to be a sign of neuronal damage or compromised metabolism (Burtscher and Holtås 2001; Gujar et al. 2005; Moffett et al. 2007).

[6] Choline-containing compounds such as glycerophosphocholine, phosphatidylcholine, and phosphocholine form part of cell membranes, and elevated levels are indicative of changing membrane composition, which could be caused for example by the demyelination of local neurons (Govindaraju et al. 2000; Gujar et al. 2005)

compared to assess any treatment-induced changes in the brain, whereas in *treatment outcome prediction* studies patients are scanned prior to treatment to determine if any parameters correlate with level of response to treatment assessed at a later date (Fullana and Simpson 2016).

A plethora of treatment mechanism studies have been conducted using a range of neuroimaging techniques (Table A.3). The OFC (Benkelfat et al. 1990; Rubin et al. 1995; Kang et al. 2003) and the caudate (Schwartz et al. 1996; Nakatani et al. 2003; Diler et al. 2004; Ho Pian et al. 2005; Apostolova et al. 2010) have emerged as areas commonly reported to undergo changes over treatment. A recent review of changes following psychotherapy ascertained that reductions in the activity of the caudate, OFC, PFC, and ACC, followed by those in the thalamus and temporal and occipital cortices were most commonly found across the literature (Thorsen et al. 2015). The efficacy of TMS of the OFC further supports its involvement in pathology of OCD (Ruffini et al. 2009).

Treatment outcome prediction studies have given similarly variable results (Shin et al. 2013; Fullana and Simpson 2016). In the first such study, left OFC activity was found to predict improved response to ERP therapy but poorer response to fluoxetine (Brody et al. 1998), and several subsequent studies have also pinpointed the OFC as a predictor region (Saxena et al. 1999; Rauch et al. 2002; Hoexter et al. 2015). Meta-analyses and reviews have supported a negative association between increased activation in ACC and OFC and improved response to SSRIs (Ball et al. 2014); the latter also predicts response to ERP (Fullana and Simpson 2016). A handful of studies have investigated predictors of response to neurosurgical treatments (Borairi and Dougherty 2011), with metabolism in the subgenual ACC and metabolism in posterior cingulate cortex as well as decreased grey matter volume in the dACC, found to predict response to anterior capsule DBS and anterior cingulotomy respectively (Rauch et al. 2001; Van Laere et al. 2006; Banks et al. 2015).

In a complementary approach to treatment outcome prediction studies, Atmaca et al. 2006 used structural MRI to compare the neural morphology of first-applying, treatment-responding and treatment-refractory OCD patients with each other and with controls and found that first-applying and treatment-refractory patients had reduced OFC and increased thalamic volumes compared to healthy controls and to treatment-responders. Other similar investigations have found reduced NAA levels in ACC in responders to SSRI+atypical psychotics as opposed to responders to SSRIs alone or nonresponders (Sumitani et al. 2007), and lower basal ganglia NAA and higher thalamic Cho levels in non-responders to pharmacotherapy as compared to responders (Mohamed et al. 2007).

1.3.1.4 Functional connectivity

fMRI studies have also identified abnormalities in resting state functional connectivity in OCD patients which have generally converged upon hyperactivity of CSTC circuits, though the precise regions of PFC and striatum identified have varied between studies. Studies have reported increased functional connectivity of the OFC (Harrison et al. 2009; Meunier et al. 2012; Harrison et al. 2013; Jung et al. 2013; Beucke et al. 2013; Hou et al. 2013; Hou et al. 2014; Bernstein et al. 2016), dorsal striatum (including caudate and putamen) (Harrison et al. 2009; Fitzgerald et al. 2011; Beucke et al. 2013; Hou et al. 2013;

Hou et al. 2014; Posner et al. 2014; Anticevic et al. 2014; Bernstein et al. 2016), and thalamus (Fitzgerald et al. 2011; Hou et al. 2013). Specific inter-relationships identified have included reduced functional connectivity between the OFC and dorsal striatum (Hou et al. 2013; Beucke et al. 2013; Bernstein et al. 2016), OFC/ventral mPFC and ventral striatum (Harrison et al. 2009; Harrison et al. 2013; Sakai et al. 2011; Jung et al. 2013 but see Posner et al. 2014), anterior/dorsolateral PFC (dlPFC) and dorsal striatum (Harrison et al. 2009; Posner et al. 2014), dlPFC and ventral striatum (Sakai et al. 2011), dorsal striatum and ACC (Fitzgerald et al. 2011), thalamus and cingulate cortex (Fitzgerald et al. 2011; Hou et al. 2013), and thalamus and dorsal caudate (Hou et al. 2013), and increased connectivity between dorsal striatum and ventral PFC (Fitzgerald et al. 2011), caudate and middle cingulate cortex (Kang et al. 2013), ventral striatum and ACC (Posner et al. 2014 but see Anticevic et al. 2014) and ventral and dorsal striatum (Posner et al. 2014), relative to healthy controls.

1.3.1.5 Structural differences

Structural MRI scanning is one of the neuroimaging techniques that has been used most frequently in OCD research, and has also yielded some of the most inconsistent results (Table A.4; Ahmed et al. 2012). Early studies were limited to the examination of pre-identified regions of interest (ROIs), chosen within the CSTC circuitry, whilst in recent years the use of voxel-based morphometry (VBM) has allowed groups to look across the whole brain in an unbiased fashion (Mechelli et al. 2005).

Findings of structural differences in the OFC in OCD have been the most variable and controversial. The area was frequently used as an ROI in early studies, and a meta-analysis of that body of work revealed consistent reductions in OFC volume (Rotge et al. 2009). Subsequent meta-analyses which focussed on VBM investigations however, have not found evidence of significant changes to the OFC (Radua and Mataix-Cols 2009; Radua et al. 2010), and it was suggested that functional imaging results with respect to the area may reflect secondary neural responses to compensate for pathology in other areas (Radua and Mataix-Cols 2009). That other meta-analyses have reported both grey matter increases (Rotge et al. 2010) and reductions (Peng et al. 2012) in the OFC, is reflective of the heterogeneity of findings in the literature. A majority of individual studies identify alterations in the OFC, but the direction of the changes is inconsistent, and various factors including drug treatment effects, lack of symptom dimension stratification, and differences in medial/lateral subregions of the OFC have been proposed to account for the variability of results (Piras et al. 2015).

Results for the other classic CSTC regions are more straightforward. Results regarding striatal alterations have been more consistent and all meta-analyses and reviews which have been conducted so far report increases in grey matter in the striatum (Rotge et al. 2009; Radua and Mataix-Cols 2009; Radua et al. 2010; Rotge et al. 2010; Peng et al. 2012; Piras et al. 2015). Specific regions of the striatum identified vary a little between individual studies, and changes have been described as occurring in the lenticular nucleus, particularly the ventral anterior putamen, extending to the caudate nucleus (Radua and Mataix-Cols 2009; Radua et al. 2010; Peng et al. 2012). Findings as regards the striatum are not limited to size but also extend to shape; Choi et al. 2007 reported outward deformities in the superior, anterior portion of the caudate and the inferior lateral portion of the left putamen. Both symptom severity and illness

duration have been found to correlate with increases in the putamen in individual studies (Pujol et al. 2004; Szeszko et al. 2008; Zarei et al. 2011; Piras et al. 2015). Thalamic findings have varied between studies, and were more consistently found in ROI work (Rotge et al. 2009). When alterations are found however, the changes comprise increased thalamic volume (Piras et al. 2015).

Other areas consistently highlighted by meta-analytic work include the cingulate cortex and regions of the PFC. Grey matter reductions are reported in the anterior cingulate/dorsal mediofrontal gyri, which extend to the supplementary motor area and the frontal eye fields, as well as the supramarginal gyrus and the dlPFC/middle frontal gyrus (Rotge et al. 2009; Radua and Mataix-Cols 2009; Radua et al. 2010; Rotge et al. 2010; Peng et al. 2012).

White matter alterations in OCD are another avenue of research, different facets of which can be investigated as part of VBM structural MRI studies, or using MRS or DTI (Table). Reductions of white matter connectivity are found in most, but not all studies, with abnormalities in the internal capsule, cingulate bundle and corpus callosum white matter tracts being widely reported (Fontenelle et al. 2009; Koch et al. 2014), though there are inconsistencies in the direction of findings, with both increased and decreased fractional anisotropy[7] being reported for the three locations in a recent meta-analysis (Piras et al. 2013). It has been suggested that increases and decreases in white matter could realistically co-exist, and would mirror the increased and decreased levels of functional connectivity that have been found (Koch et al. 2014).

In the largest study to date, a multicentre "mega-analysis", OCD patients were ascertained to have reduced volumes of the dorsomedial PFC, ACC and the inferior frontal gyrus extending to the anterior insula (Wit et al. 2014).

1.3.1.6 OCD patient stratification

OCD is a clinically heterogeneous disorder and the lack of stratification of patient samples, for example by variables such as age, sex, age of onset, treatment status and history, illness duration, comorbidities and most importantly symptom dimensions, is a widespread issue across the spectrum of OCD research which has been discussed in developmental, genetic, imaging and therapeutic research contexts (Kwon et al. 2009; Abramovitch et al. 2012; Fan and Xiao 2013; O'Neill and Feusner 2015; Mattina and Steiner 2016). Whilst the majority of neuroimaging studies of OCD have treated the disorder as a unitary nosological entity, some have attempted to resolve the neural basis of OCD, using both functional and structural imaging, for different patient subgroups, particularly along the lines of symptom dimensions (§1.2.3.1; Leckman et al. 2009).

In an fMRI symptom provocation paradigm of patients with mixed obsessions, dimensionally specific stimuli elicited activation in distinct neural circuits; associations included washing stimuli and the ventromedial PFC (vmPFC) and right caudate, checking stimuli and the putamen/globus pallidus, thalamus and dorsal cortical areas including the ACC, and hoarding stimuli and the left precentral gyrus and the

[7] A measure thought to reflect the degree of myelination or organisation of fibres, with and thus putatively functional hyperconnectivity as fractional anisotropy increases (Ayling et al. 2012; Piras et al. 2013)

right OFC (Mataix-Cols et al. 2004). Similarly, disgust paradigms have been used to compare activation patterns in those with checking and washing obsessions. Washing obsessions have been found to modulate ventrolateral PFC (vlPFC) activation in response to disgust (Lawrence et al. 2007), and when shown washing-related disgust-inducing stimuli, washers displayed activation in the insula, an area thought to be associated with disgust, whereas checkers showed activation in fronto-striatal regions (Phillips et al. 2000).

Other cognitive tasks have also been used to investigate dimension-specific neural activation. During a continuous performance task, "forbidden thoughts factor" symptoms (§1.2.3.1) correlated positively with activity in the striatum and negatively with activity in the right parietal cortex, while symmetry factor symptoms correlated negatively with activity in the left middle temporal gyrus and left temporoinsular cortex, and cleaning factor symptoms correlated with anterior cingulate cortex and left OFC activity (Rauch et al. 1998). Moreover, when tested on the serial reaction time task, patients with forbidden thoughts symptoms show increased activation of the left OFC, while symptom severity with respect to the symmetry or cleaning factors, was negatively correlated with recruitment of the right striatum (Rauch et al. 2007).

Symptom dimensions have also been linked to specific brain regions in structural studies, including in a plethora of VBM studies. Valente et al. 2005 found that symmetry symptoms positively and negatively correlated with left lateral OFC and left dACC, and with right posteroventral OFC and right dorsomedial and pulvinar thalamic nuclei grey matter volumes respectively, and forbidden thoughts symptoms positively correlated with grey matter volumes in the right posterior cingulate and the medial occipital, while Pujol et al. 2004 showed aggressive obsessions and checking compulsions negatively correlate with amygdala grey matter volume. Heuvel et al. 2009 showed that cleaning factor symptoms correlated negatively with caudate grey and right parietal white matter volumes, symmetry factor symptoms correlated negatively with global grey and white matter, and right motor cortex, left insula and left parietal cortex grey matter volumes and harm and checking symptoms were negatively correlated with temporal lobe grey and white matter volumes. Furthermore Alvarenga et al. 2012 showed that aggressive symptoms positively correlated with grey matter volumes in lateral parietal cortex and negatively correlated with volumes in the insula, left putamen and left inferior OFC, and sexual/religious scores positively correlated with volumes in the right middle lateral OFC and right dlPFC and negatively correlated with bilateral ACC.

Neural correlates associated with early- and late-onset OCD subtypes have also been investigated. Early-onset OCD patients showed reduced rCBF in the right thalamus, left perigenual ACC (pgACC) and in the inferior lateral PFC relative to late-onset patients (Busatto et al. 2001). Relative to controls, only early-onset patients showed reduced left dACC and right cerebellar rCBF and only late-onset patients showed decreased left precuneus rCBF, whilst both groups had reduced lateral OFC rCBF (Busatto et al. 2001). Another group demonstrated that reduced left occipital and increased left medial frontal grey matter, as well as reduced right parietal and increased left frontal white matter were associated with early-onset OCD (Kopřivová et al. 2009).

1.3.2 Summary of neuroimaging findings and conclusions

Hundreds of neuroimaging studies have attempted to ascertain the neural basis of OCD, and as a result of this intensive level of research OCD has one of the best evidenced and elaborated neurobiological theories of any of the psychiatric disorders, that of dysfunction in the limbic CSTC loop that includes the OFC and caudate. In general, the data support this classic theory, despite variability in findings which cloud the overall picture (Insel 1992; Kwon et al. 2009), but results also consistently implicate additional areas such as the ACC and the amygdala, which have been subsequently incorporated into an extended model of fronto-striatal dysfunction. However, a lack of patient stratification is rife in OCD imaging, both in terms of parameters common to all psychiatric disorders such as treatment status and history, and also regarding factors unique to OCD as a result of its striking heterogeneity, such as symptom dimensions and age of onset. Thus whilst the evidence accumulated so far is useful and illuminating, further work is needed, both in more refined neuroimaging investigations, and in complementary studies utilising techniques other than imaging, such as animal research.

There have been several noteworthy animal studies into the neural underpinnings of compulsivity which have complemented the findings from OCD neuroimaging, such as the *Sapap3*[8] and *Slitrk5*[9] knockout mouse models (Ting and Feng 2011). In both models, knockout of the relevant gene induces compulsive behaviour which can be ameliorated with SSRI treatment, as well as corticostriatal abnormalities (Welch et al. 2007; Shmelkov et al. 2010); *Sapap3* mutants develop defects in corticostriatal synapses which are also rescuable with SSRIs (Welch et al. 2007), while *Slitrk5* knockouts show hyperactivation of the OFC and anatomical and morphological abnormalities of neurons in the striatum (Shmelkov et al. 2010). Further evidence of the involvement of corticostriatal circuitry in compulsive behaviour has stemmed from the advent of optogenetics (Rauch and Carlezon 2013). The repeated hyperactivation of the OFC-ventromedial striatum over several days was reported to produce compulsive grooming in mice which could be remediated by chronic fluoxetine (Ahmari et al. 2013). Contemporaneously, Burguière et al. 2013 demonstrated that stimulation of the lateral OFC and its striatal terminals increased inhibition of striatal medium spiny neurons and reduced the compulsive behaviours of *Sapap3* mutant mice.

Though the limitations of animal studies such as the above are clear, for example the debatable face validity of compulsive grooming in mice to human OCD, they do provide a window into the *causality* of such behaviour. Neuroimaging studies are by their nature correlative, and cannot definitively establish whether neural differences between OCD patients and healthy controls are the cause of OCD symptoms, or develop as a result of the disorder. The exceedingly long delay between the initial onset of OCD and the point at which patients seek help (§1.2.3.5), and thus become available to be included in imaging studies, means that the issue, which is a known general limitation of psychiatric neuroimaging, is particularly relevant to the study of OCD. The problem underscores the need for a multi-faceted approach to the study of OCD which goes beyond neuroimaging.

For such a multi-faceted approach to the study of OCD to be successful it must include an understanding of the psychology of the disorder. It is now undeniable that there is a significant biological component to

[8] Synapse-associated protein 90/postsynaptic density protein 95-associated protein 3 (SAPAP3) is a postsynaptic scaffolding protein found at excitatory synapses (Welch et al. 2004).

[9] SLIT and NTRK-like protein 5 is a transmembrane protein specific to neurons (Aruga and Mikoshiba 2003).

OCD, but neither OCD nor any other psychiatric disorder can be truly understood in terms of neurobiology alone. Unlike in physical illness, many of the subjective symptoms, experiences and feelings that form part of psychiatric disorders do not readily map onto physical correlates and can thus only be captured by the consideration of their psychological basis. Greater psychological knowledge of a disorder can also help inform pharmaceutical research; the identification of deficiencies in particular psychological processes within a disorder can, with an appreciation of the neurobiology of such processes, inform researchers of potential drug targets. Finally, in clinical practice, psychological impairments can also provide a useful assay of treatment response (Clark and Robbins 2009). Hence the psychology of OCD is a vital strand of the comprehension of this disease, and is described in the next section.

1.4 Psychological conceptualisations of compulsivity

1.4.1 OCD as an archetypal disorder of compulsivity

OCD is the archetypal disorder of compulsivity, a neurocognitive trait defined as "the performance of repetitive and functionally impairing overt or covert behavior without adaptive function, performed in a habitual or stereotyped fashion, either according to rigid rules or as a means of avoiding perceived negative consequences" (Fineberg et al. 2014). The broad trait of compulsivity can be deconstructed and conceptualised as the product of multiple distinct neurocognitive domains (Fineberg et al. 2010; 2014). These domains can be grouped into two major psychological categories: dysfunction in processes that comprise different aspects of *cognitive flexibility*, and aberrant *habit learning*.

1.4.2 Compulsivity as cognitive inflexibility

Cognitive flexibility can be defined as "the ability to shift between mental processes in order to respond to situations in different ways" (Eslinger and Grattan 1993; Dajani and Uddin 2015). In a dynamic environment, animals and humans need to be able to assess changing environmental contexts and contingencies and then quickly alter their behaviour either to maximise beneficial outcomes or to avoid negative ones, and also to adapt to novel situations (Easton 2005). It is thus unsurprising that cognitive flexibility has been linked to superior functioning and outcomes in humans across a range of domains such as learning, social ability, emotion regulation and psychiatric prognosis (Martin and Anderson 1998; Bonino and Cattelino 1999; Qouta et al. 2001; Davis et al. 2010; Martin et al. 2011; Genet and Siemer 2011; Engel de Abreu et al. 2014; Chen et al. 2014; Keith et al. 2015; Hendricks and Buchanan 2016). Cognitive flexibility has been investigated using a range of paradigms, each of which measure different psychological facets of the construct. These include reversal learning, attentional set shifting and task switching (Kehagia et al. 2010; Cools 2015; Dajani and Uddin 2015).

1.4.2.1 Reversal learning as an assay of cognitive inflexibility

Reversal learning is a well-validated and widely used assay of cognitive flexibility or its lack thereof, and hence also of compulsivity (Robbins et al. 2012b; Izquierdo and Jentsch 2012; Cools 2015). In a typical task design, subjects are exposed to two stimuli, one of which is associated with reward, and one of

which is not linked to an outcome or is linked to punishment (Clarke and Roberts 2011). To increase the level of difficulty paradigms can be made probabilistic, where negative feedback is given in response to a proportion of correct responses (Cools et al. 2002). Subjects learn to discriminate and to preferentially interact with the rewarded stimulus. The stimulus-outcome contingencies are then reversed, such that the stimulus which was previously rewarded ceases to be, and the formerly unrewarded stimulus is now rewarded. Subjects have to interpret feedback to inhibit responding to the previously correct stimulus and switch their responding to the newly correct one.

1.4.2.2 Reversal learning, cognitive flexibility and OCD

OCD patients show only mild impairments in tests of reversal learning. Reports differ between studies, with some authors reporting reduced numbers of correct errors relative to control subjects (Remijnse et al. 2006), and others only slower response times (Chamberlain et al. 2008; Valerius et al. 2008; Remijnse et al. 2009) which may correlate with symptom severity (Valerius et al. 2008), and some not reporting any behavioural impairment at all (Chamberlain et al. 2007a). In a go/no-go reversal test however, OCD patients did show a perseverative deficit of an increased switch cost (Watkins et al. 2005). The variability in manifestation of reversal learning impairments in patient samples may be a result of blunting of the expression of cognitive flexibility deficits in neuropsychological testing by the preponderance of individuals who had received medication (usually SSRIs, consistent with the serotonin hypothesis of OCD (§1.5.1)) and other treatment prior to being tested. More consistent are the reports of abnormal neural recruitment during the task relative to controls[10]. Multiple groups have found reduced OFC activity (Remijnse et al. 2006; 2009; Chamberlain et al. 2008; Freyer et al. 2011), which have been further specified to present particularly in the lateral part (Remijnse et al. 2006; 2009; Chamberlain et al. 2008), but also in medial, anterior and posterior regions (Remijnse et al. 2006; 2009). OCD patients also show reduced striatal recruitment relative to controls, with reports of reduced activity in the caudate (Remijnse et al. 2006; 2009)[11] and putamen (Freyer et al. 2011). Other brain regions reported to be under-activated in OCD during reversal learning include the insula, dlPFC, ACC and parietal cortex (Remijnse et al. 2006; 2009; Chamberlain et al. 2008).

OCD patients have also displayed impaired cognitive flexibility in other paradigms. The test of set-shifting that has been most frequently applied to OCD subjects is the Wisconsin Card Sorting Test (WCST; Berg 1948; Eling et al. 2008; Nyhus and Barceló 2009). In the WCST subjects have to sort a deck of cards upon which symbols are printed, according to a rule that they must learn by trial and error across the test. Each card contains between one and four examples of one type of symbol in a single colour. There are four available symbols, circles, stars, squares or crosses, and four available colours, red, green blue or yellow. Thus there are three different ways in which the cards can be sorted into four distinct categories and only one of the three ways is correct at any one time. The subjects are given stimulus cards at the beginning of the test and must match their deck of cards to those stimulus cards, receiving feedback after the placement of each card as to whether their chosen categorisation was correct. The rule is changed to one of the other

[10] Neural recruitment during reversal learning has been shown to have high rest-retest reliability and has thus been suggested to be a useful marker of the course of the disorder (Freyer et al. 2009).

[11] In Remijnse et al. 2009, OCD patients showed underactivation of the caudate during receipt of reward, but increased activation during affective switching.

possible categorisation schemes following ten consecutive correct responses by a subject, at which point the subject must stop using the previous rule and adopt the new one, a process which requires cognitive flexibility.

Despite its repeated administration to OCD patients, there have been inconsistent results regarding the WCST and OCD (Olley et al. 2007); there are numerous reports of deficits (Head et al. 1989; Hymas et al. 1991; Gambini et al. 1993; Gross-Isseroff et al. 1996; Okasha et al. 2000; Lacerda et al. 2003; Roh et al. 2005; Boldrini et al. 2005; Bohne et al. 2005; Aigner et al. 2005; Bannon et al. 2006; Andrés et al. 2007; Shin et al. 2008; Cavedini et al. 2010; Rajender et al. 2011; Kashyap et al. 2012a; Ghassemzadeh et al. 2012; Tükel et al. 2012) but also many of normal performance in OCD patients relative to controls (Abbruzzese et al. 1995a; b; 1997; Cavedini et al. 1998; Moritz et al. 2002; Cavallaro et al. 2003; Roth et al. 2004; Fenger et al. 2005; Grisham et al. 2009; Ornstein et al. 2010; Kohli et al. 2015). Individuals with subclinical obsessive-compulsive symptoms are also impaired on the WCST (Goodwin and Sher 1992; Kim et al. 2009; Sternheim et al. 2014 but see Johansen and Dittrich 2013), as were unaffected relatives of OCD patients (Cavedini et al. 2010; Rajender et al. 2011). A meta-analysis found a small but significant difference between OCD patients and controls overall (Henry 2006), and symmetry and ordering obsessions have been shown to correlate with poorer task performance (Lawrence et al. 2006).

The WCST has been adapted for use in rhesus monkeys by two different groups to form the Conceptual Set-Shifting Task (CSST; Moore et al. 2002; Moore et al. 2003; 2005; 2006; Moore et al. 2009; Luebke et al. 2004; Moss et al. 2007; Voytko et al. 2009) and an analogue of the WCST (Mansouri and Tanaka 2002; Mansouri and Tanaka 2003; Mansouri 2006; Mansouri et al. 2007; Buckley et al. 2009a; Kuwabara et al. 2014), with the latter incorporating trial by trial matching behaviour and thus forming a closer approximation to the human paradigm. Using the latter paradigm, it has been shown that lesions of the OFC induce impairments characterised by difficulty in responding correctly and maintaining such correct responding after committing single or low numbers of correct trials, data which the authors interpreted as being indicative of a role for the region in representing and updating the value of different rules (Buckley et al. 2009a).

Another task commonly used to assess cognitive flexibility is that of attentional set-shifting, in which subjects are given a discriminative set formed of stimuli with multiple perceptual dimensions, e.g. compound visual stimuli formed of lines superimposed upon shapes, only one of which is relevant to the discrimination at any one time. Subjects first acquire the discrimination by attending to the perceptual dimension which is initially linked to reward and are subsequently required to shift their attentional set to a previously irrelevant perceptual dimension when that dimension becomes informative of reward availability, and the previously informative dimension becomes irrelevant (Nilsson et al. 2015; Oikonomidis et al. 2016). Attentional set shifting is often implemented using the CANTAB neuropsychological testing battery, in which it forms part of the intra-dimensional/extra-dimensional (ID/ED) set-shifting task (Downes et al. 1989; Sahakian and Owen 1992; Fray et al. 1996; Nilsson et al. 2015), a paradigm which has been adapted for several different species (Dias et al. 1996a; b; 1997; Weed et al. 1999; Birrell and Brown 2000; Brigman et al. 2005; Garner et al. 2006; Morton and Avanzo 2011; Wright Jr et al. 2013; Scheggia et al. 2014; Scheggia and Papaleo 2016). The situation as regards intra-dimensional/extra-dimensional (ID/ED) set-shifting in OCD is clearer than that of the WCST (Kuelz et al. 2004), with findings of deficits

in most studies (Veale et al. 1996; Purcell et al. 1998a; Watkins et al. 2005; Fenger et al. 2005; Chamberlain et al. 2007b; Rao et al. 2008; Vaghi et al. 2016 but see Purcell et al. 1998b; Nielen and Den Boer 2003). In addition, poorer performance in ID/ED shifting has also recently been linked to obsessive-compulsive symptoms in non-clinical populations (Francazio and Flessner 2014; Chamberlain et al. 2016). Mixed results were also found in other set-shifting tasks such as the Trail Making Test[12] (deficits: Penadés et al. 2005; Roh et al. 2005; no deficits: Schmidtke et al. 1998).

In the object alternation task (OAT), subjects are given two objects and told that they must choose between them in order to find the object beneath which money is hidden, and that they must do this on every trial. Unbeknownst to the subject, both objects are correct in the initial trial and on the second trial the object not initially chosen by the subject becomes correct. From this point forward, if the subject chooses the correct object the position of the money is switched and is placed beneath the other object, and if the subject chooses the incorrect object the position of the money remains the same, such that subjects must learn to alternate their choice of objects in order to maximise the accumulation of money (Hoffman 2016). The task thus has similarities to a standard reversal learning paradigm. OCD patients reliably show perseverative deficits in the OAT (Abbruzzese et al. 1995a; 1997; Gross-Isseroff et al. 1996; Cavedini et al. 1998; Aycicegi et al. 2003; Harris and Dinn 2003 but see Bohne et al. 2005), as do individuals with subclinical OCD symptoms (Spitznagel and Suhr 2002). The paradigm has also been shown to be sensitive to OFC dysfunction (Pribram and Mishkin 1956; Mishkin et al. 1969).

Neuroimaging of cognitive flexibility tasks other than reversal learning have concurred with the reversal learning data. During a visual-spatial switching task requiring an extradimensional shift, adolescent patients showed a negative correlation between switch cost and right caudate activation, in contrast to the positive correlation of control subjects, and also showed reduced recruitment of the left inferior frontal gyrus (Britton et al. 2010), while in an ID/ED set-shifting task it was found that reduced functional connectivity between the caudate and the vlPFC was associated with poorer task performance (Vaghi et al. 2016). In a series of experiments using a task-switching paradigm based on the Meiran switch task[13], OCD patients showed underactivation in the inferior frontal regions, middle frontal gyrus, ACC, caudate, thalamus, parietal and cerebellar cortex (Woolley et al. 2008; Page et al. 2009; Rubia et al. 2010). Two further studies revealed that OCD patients were impaired in the performance of task-switching paradigms (Gu et al. 2008; Remijnse et al. 2013), with findings of reduced recruitment of dlPFC, ACC, the caudate nucleus, vmPFC and the right OFC in the first (Gu et al. 2008) and increased recruitment of the putamen, ACC and insula and reduced recruitment of the anterior PFC in the second (Remijnse et al. 2013). Furthermore, it has been shown that the abnormal recruitment seen during task-switching normalises with symptom improvement (Vriend et al. 2013). Lastly, OCD patients were recently examined in a novel shifting go/no-go

[12] The Trail Making Test is a paradigm formed of two parts; in part A subjects must draw lines to join numbers distributed across a piece of paper in sequential order and in part B the subject must alternate between letters and numbers (Tombaugh 2004). Part B has been shown to depend upon, among other abilities, task-switching performance (Crowe 1998; Sánchez-Cubillo et al. 2009).

[13] The task-switching paradigm, based upon the original design by Meiran 1996 and adapted for use in fMRI studies (Smith et al. 2004; Smith et al. 2006; Rubia et al. 2006), comprised the presentation of four white circles in a two-by-two square grid, with a double-headed arrow in the centre of the grid that could be aligned either horizontally or vertically. Subjects were also given a keypad with four buttons corresponding to up, down, left and right directions. On each trial one of the white circles would turn red, and based upon the orientation of the central arrow, subjects had to choose the corresponding direction of their keypad that matched the location of the red circle in the grid. Across the task the orientation of the central arrow was switched back and forth so that subjects had to switch their attention between the vertical and horizontal dimensions of the grid.

task, and whilst they exhibited no behavioural impairment, patients did show reduced activation of the inferior parietal and inferior frontal cortex, the striatum and the occipital cortex (Morein-Zamir et al. 2016)

Finally, meta-analyses and reviews which have considered the results of a range of cognitive flexibility paradigms have determined that cognitive flexibility is impaired in OCD (Abramovitch et al. 2013; Shin et al. 2014; Snyder et al. 2015; Gruner and Pittenger 2016; Gonçalves et al. 2016), though it has been suggested by some, based upon findings of impairments in neuropsychological tasks unrelated to cognitive flexibility (e.g. Purcell et al. 1998a; b), that these cognitive flexibility deficits are part of a larger impairment in general executive functioning which may not be strictly limited to cognitive flexibility (Abramovitch et al. 2013; Shin et al. 2014; Snyder et al. 2015). In this thesis, reversal learning was chosen as the task with which to investigate the neural basis of cognitive flexibility, despite the relatively mild deficits exhibited by OCD patients. The decision to use reversal learning was the result of a number of practical factors such as how readily the task could be translated into a form suitable for marmosets, as well as the correlation of the regions found to be crucial to reversal learning in the animal literature (§1.4.2.3) and those commonly identified as neuroanatomical substrates of OCD (§1.3). All tasks of cognitive flexibility have shown variability in patient samples, which may be a result, as previously described, of the serotoninergic treatment history of many of the individuals that have been tested.

1.4.2.3 Neuroanatomical substrates of reversal learning

A substantial body of data exists on the involvement of the fronto-striatal circuitry in reversal learning. Lesions and inactivations of the OFC in mice (Bissonette et al. 2008; Graybeal et al. 2011), rats (Ferry et al. 2000; Schoenbaum et al. 2002; Schoenbaum et al. 2003b; Chudasama and Robbins 2003; McAlonan and Brown 2003; Bohn et al. 2003; Kim and Ragozzino 2005; Ghods-Sharifi et al. 2008; Churchwell et al. 2009; Izquierdo et al. 2013), cats (Teitelbaum 1964), monkeys (Butter 1969; Jones and Mishkin 1972; Dias et al. 1996a; Meunier et al. 1997; Izquierdo et al. 2004; Rudebeck and Murray 2008; Rygula et al. 2010 but see Rudebeck et al. 2013[14]) and humans (Rolls et al. 1994; Fellows and Farah 2003; Hornak et al. 2004; Berlin et al. 2004; Tsuchida et al. 2010), give deficits in reversal learning, as do lesions of the striatum (Divac et al. 1967; Kirkby 1969; Kolb 1977; Pisa and Cyr 1990; Clarke et al. 2008; Castañé et al. 2010). Furthermore, c-Fos expression, a marker of neuronal activity (Bullitt 1990; Hoffman et al. 1993), has been shown to increase in the OFC during reversal learning (Brigman et al. 2013). Intra-OFC administration of a GluN2B antagonist, which had previously been found to impair reversal learning when given systemically (Dalton et al. 2011), also impaired reversal learning (Brigman et al. 2013).

[14]The recent findings of Rudebeck et al. 2013 do not, in contrast to the wealth of studies described above, support a role for anterior OFC in reversal learning. Excitotoxic lesions of the region did not induce a deficit in object reversal learning, contradicting previous results achieved with aspiration lesions in the species (Butter 1969; Iversen and Mishkin 1970; Jones and Mishkin 1972; Izquierdo et al. 2004). An impairment in object reversal learning was instead induced by the aspiration of a narrow strip of cortex in the posterior OFC, a result interpreted by the authors as evidence that it was damage to fibres of passage within the OFC that had previously been the driver of reversal learning deficits (Rudebeck et al. 2013). This result is more difficult to assimilate when considered in light of impairments in reversal learning that have followed excitotoxic lesions of the OFC in rats (Ferry et al. 2000; Schoenbaum et al. 2002; Schoenbaum et al. 2003b; Chudasama and Robbins 2003; McAlonan and Brown 2003; Bohn et al. 2003; Izquierdo et al. 2013) and in marmoset monkeys (Dias et al. 1996a). Whether differing findings between rhesus macaques, rats and marmoset monkeys are due to species or task differences, or other factors that have yet to be identified, is currently difficult to assess, and should be the subject of future investigations.

Functional imaging also supports the role of the OFC in reversal learning. The OFC is activated during reversal learning in healthy people (Kringelbach and Rolls 2003; O'Doherty et al. 2003), with a more recent finding pinpointing the area of importance as the lateral part of the OFC (Ghahremani et al. 2010). The latter result is further supported by the report that DBS of the lateral OFC in rats impairs reversal learning (Klanker et al. 2013b). There have also been attempts to fractionate reversal learning and to assign different components of the process to different regions of the OFC. In an early review of neuroimaging studies, it was suggested that the medial OFC was involved with the online monitoring of outcome values and their associations with stimuli and that the lateral OFC was particularly needed for the suppression of responding to previously rewarded stimuli (Elliott et al. 2000). Alternatively, Hampshire and Owen stated that the lateral OFC was involved in reversal learning using negative feedback and the medial OFC used for reversals with positive feedback (Hampshire and Owen 2006), which agreed with previous reports of recruitment of lateral and medial OFC during reversal learning after punishing and rewarding outcomes respectively (O'Doherty et al. 2001 but see O'Doherty et al. 2003). This was slightly revised more recently when the authors proposed that the lateral OFC mediated the implementation of reversals and the medial OFC the positive affect generated by feedback (Hampshire et al. 2012). As well as its involvement in instrumental reversal learning, the OFC has also been implicated in reversal of Pavlovian conditioning (Morris and Dolan 2004).

Animal studies have also suggested that there may be a lateromedial distinction in the way in which parts of the OFC contribute to reversal learning, though the evidence is conflicting and the results difficult to reconcile with one another. A recent rodent study comparing different areas of the PFC found that inactivation of the the lateral OFC of the rat induced reversal impairments while inactivation of the medial OFC led to a broader set of impairments which included general discriminative problems, increased perseveration and deficits in sensitivity to both positive and negative feedback (Dalton et al. 2016). These results contrast with the much earlier findings that in macaques, lesions of the lateral OFC extending to the inferior frontal convexity induced a perseverative reversal learning impairment which was only present for the first reversal whilst lesions of the medial OFC caused non-perseverative deficits that were only shown on the second and subsequent reversals (Iversen and Mishkin 1970). Finally, there have also been negative findings as regards the effect of lesions of subregions of the OFC on reversal learning. Some groups have not found reversal learning impairments in rhesus macaques following selective lesions of the lateral OFC (Kazama and Bachevalier 2009; Rudebeck and Murray 2011) or the medial OFC (Rudebeck and Murray 2011).

There are several theories about the psychological underpinnings of the OFC lesion-induced reversal learning deficit. These include problems with response inhibition, the generation of flexible stimulus-reward associations, encoding outcome expectancies or with credit assignment. The rationale for each proposed theory can be described, but two factors, the variation of circumscribed anatomical regions of the OFC which result in a deficit, and the differing profile of deficits produced (e.g. perseverative or non-perseverative), have led to the suggestion that the OFC reversal learning deficit is not a unitary entity, and is likely composed of the disruption of several underlying psychological processes (Clarke and Roberts 2011).

That OFC lesions impaired the inhibition of responses to a previously rewarded stimulus is an explana-

tion of the lesion deficit first suggested in an early study (Mishkin 1964). It is perhaps the simplest theory, and is the most parsimonious with the exhibition of *perseverative* behaviour, i.e. repetitive responding to a previously correct stimulus, seen in some reversal learning studies (e.g. Clarke et al. 2004) and long associated with frontal lobe damage in humans (Stuss and Benson 1984). It can also be applied to OFC lesion-induced deficits in detour reaching[15] (Wallis et al. 2001) and the 5-choice serial reaction time[16] and stop-signal reaction time tasks[17] (Chudasama et al. 2003; Eagle et al. 2008), and in altered behaviour during the delayed reward task (Winstanley et al. 2004). In opposition to this theory however, is evidence that OFC lesions do not impair the ability to inhibit previously advantageous but currently inappropriate responding for reward in other contexts, such as the prepotent urge to select the larger of two food quantities in the reversed reward contingency task[18] (Chudasama et al. 2007). Moreover, OFC lesions can impair task performance by inducing increased responding to irrelevant stimuli, not just to those which had previously been rewarded (Kim and Ragozzino 2005).

The encoding of flexible stimulus-reward associations, which are updated and altered when stimulus-outcome contingencies change, is another popular theory of OFC function (Rolls 2000; 2004; Rolls and Grabenhorst 2008), impairment in which has been construed to cause the OFC reversal learning deficits. Electrophysiological experiments in which it was found that a subset of cue-selective neurons in the OFC reverse their selectivity during reversal learning initially supported this idea (Thorpe et al. 1983; Rolls et al. 1996; Schoenbaum et al. 1999; 2003, a). However, further analyses of electrophysiological data dispute the theory (Schoenbaum et al. 2009; Stalnaker et al. 2009). Firstly, there exist other brain regions, such as the amygdala, which contain a higher proportion of neurons which reverse their cue-selectivity than that of the OFC and do so more rapidly (Saddoris et al. 2005; Paton et al. 2006), though this may only hold true for neurons coding negative not positive valence (Morrison et al. 2011). Secondly, better reversal learning does not correlate with greater reversal of the cue-selectivity of OFC neurons as one might expect, instead the opposite is true - rats and mice reverse more slowly when there is more rapid reversal of encoding in the OFC (Schoenbaum et al. 2006; Stalnaker et al. 2006; Bissonette et al. 2015). As an aside, it should be noted that recent work has found that in mice with deficient expression of parvalbumin-expressing interneurons, which show impairments in reversal learning, OFC associative encoding was diminished and the relationship between reversal learning performance and OFC activity was absent, prompting the suggestion that parvalbumin-expressing interneurons contribute to the role of the OFC in reversal learning (Bissonette et al. 2015).

[15] In the detour reaching task marmosets were required to reach around the left and right sides of a transparent perspex box to gain reward, rather than reaching for the visible food directly (Wallis et al. 2001).

[16] In the 5-choice serial reaction time task animals are typically presented with five stimuli which can be illuminated/highlighted. In order to receive reward animals must correctly respond to those stimuli that have been illuminated/highlighted, and must also withhold their responding for an interval between each trial. The difficulty of the task varies with the length of time for which the stimuli are illuminated/highlighted. The task, an analogue of the human continuous performance task, has been in widespread use since the 1980s to elucidate the neural and pharmacological mechanisms behind aspects of attention and impulsivity (Robbins 2002).

[17] In stop-signal reaction time tasks participants are trained to perform a particular action, such as reporting the identity of a stimulus which is presented. Superimposed upon that behaviour, the subjects occasionally receive "stop" signals which convey that they must inhibit this response (Logan 1994; Verbruggen and Logan 2008).

[18] In the reversed reward contingency task animals must choose between a small and large quantity of food. If the animal chooses the small quantity they will actually receive the large quantity and vice versa, making the adaptive response the choice of the small quantity of food against a prepotent urge to choose the large quantity. The task was originally developed in chimpanzees (Boysen and Berntson 1995; Boysen et al. 1996; 1999; 2001), and has since been conducted with a variety of species of non-human primate (Silberberg and Fujita 1996; Anderson et al. 2000; 2008; Kralik et al. 2002; Genty et al. 2004; 2011; Murray et al. 2005).

A third perspective on OFC function is that the region encodes outcome expectancies, i.e. the characteristics and value of outcomes given particular cues from the environment (Schoenbaum and Roesch 2005; Schoenbaum et al. 2009; Schoenbaum and Esber 2010). This information is then used by other brain areas to compute prediction errors, such as dopamine neurons in the SNr and VTA, which allow learning and behavioural modification to take place in situations such as reversal learning. The vast literature linking the OFC to the encoding of value supports this theory (Tremblay and Schultz 1999; Wallis and Miller 2003; Padoa-Schioppa and Assad 2006; 2008; Hare et al. 2008; 2009; 2010; O'Doherty 2011). Moreover, the necessity of an intact OFC for normal performance in Pavlovian reinforcer devaluation (Gallagher et al. 1999; Pickens et al. 2003; 2005), Pavlovian-to-instrumental transfer (Ostlund and Balleine 2007), and inter-temporal choice (Mobini et al. 2002; Kheramin et al. 2002; 2003; Winstanley et al. 2004; Rudebeck et al. 2006), paradigms in which the contingency between the cue and the outcome is stable, also fits better with an outcome expectancy rather than flexible stimulus-reward association account of OFC function (Schoenbaum et al. 2009). However, it was recently shown that lesions of the lateral OFC, specifically areas 11 and 13, impaired reinforcer devaluation but not reversal learning (Kazama and Bachevalier 2009), raising the question of why, if the faulty encoding of outcome expectancies was supposedly responsible for both deficits, reversal learning was spared in this case (Clarke and Roberts 2011). In contrast, another recent study utilising reversals imposed with different frequencies supported the outcome expectancy theory. In low frequency reversals, greater exposure to each stimulus-outcome contingency would be expected to induce a stronger outcome expectancy, leading to a larger prediction error upon reversal whilst in high frequency reversals rapidly changing stimulus-outcome contingencies would result in small outcome expectancies and concomitantly smaller prediction errors. Given that the outcome expectancy would be formed from information integrated over time, and thus over multiple reversals in the high reversal frequency condition, the resulting signal could even hinder reversal compared to the use of immediate contingency changes. OFC lesions of rats impaired performance on low frequency reversals but improved performance on high frequency reversals, as predicted by this reasoning (Riceberg and Shapiro 2012).

Related to the concept of outcome expectancy is that of credit assignment, whereby it is held that the OFC is involved in learning specific stimulus/action-outcome contingencies by determining which of the choices made by the animal is responsible for a given outcome (Noonan et al. 2012). When contingencies are relatively stable, mechanisms using areas other than the OFC can be used to approximate links between stimuli and outcomes using the integrated history of choices and outcomes[19], but when reward contingencies change, such as during reversal, the OFC is needed to correctly assign credit using specific stimulus/action-outcome links – reasoning which may explain intact discriminative capabilities but impaired reversal learning in OFC-lesioned animals (Walton et al. 2010). A range of behavioural analyses have supported the theory that credit assignment is localised to the lateral OFC (Walton et al. 2010; Noonan et al. 2010; Noonan et al. 2011; Chau et al. 2015; Akaishi et al. 2016).

[19] Outcomes reinforce those stimuli/actions which caused them (Thorndike 1911), but also reinforce other stimuli/actions which may not be contingently linked but merely contiguous to the outcome, either in the recent past or directly following the outcome, in what is termed the *spread-of-effect* (Thorndike 1933). The spread-of-effect occurs in all animals, but in those with an intact OFC would be drastically outweighed by the influence of specific stimuli/action-outcome contingencies (Walton et al. 2010). A similar conceptualisation to the spread-of-effect is that of eligibility traces (Seo and Lee 2010).

1.4.3 Compulsivity as an imbalance between goal-directed actions and habits

Instrumental behaviour is thought to be under the control of two psychological processes: a goal-directed mechanism whereby links are made between actions and their outcomes, and a habit-based system in which stimulus-response associations are formed (Dickinson 1985). Thus habit and goal-directed actions can be defined as differing in the extent to which they are controlled by outcome expectancies; in contrast to goal-directed actions, habits are controlled by antecedent stimuli rather than outcomes (Yin and Knowlton 2006) and can thus be termed reflexive rather than reflective (Dolan and Dayan 2013). Behaviour is initially performed to achieve a desired result given particular environmental needs, i.e. is goal-directed, but over time can become automatic or habitual with practice and repetition. This transfer of control of behaviour is adaptive and reduces cognitive load; animals and humans can carry out tasks while their concentration is elsewhere, allowing the completion of multiple tasks quickly and efficiently. When situational variables change, control of behaviours that have become habitual can be transferred back to the goal-directed action system as needed. An example is learning to drive and becoming a seasoned driver over time, only to have to adapt to driving on a different side of the road when travelling abroad.

The control of instrumental behaviour has also been conceptualised computationally, within the field of reinforcement learning (Sutton and Barto 1998), as a dichotomy between *model-based* and *model-free* control (Daw et al. 2006; Dayan and Niv 2008; Dolan and Dayan 2013). In model-based behaviour, the organism forms an internal model of the environment such that the array of potential outcomes, or utilities in RL parlance, can be analysed and the optimal action chosen. Conversely, in model-free behaviour, temporal difference prediction errors are used to determine the course of action, based upon situations that have previously been experienced. Model-based control is computationally intensive, and can thus be slow, but is much more flexible compared to the retrospective dependence on cached values of previous outcomes of its model-free counterpart (Keramati et al. 2011; Dolan and Dayan 2013; Kool et al. 2016). Since their inception, model-based and model-free forms of control have been thought to be analogous to goal-directed actions and habits (Dayan and Niv 2008; Daw et al. 2011), but that assumption had not been directly tested until recently (Gillan et al. 2016c), in experiments which applied tasks used to assess goal-directed action and those based upon model-based learning to the same cohort of subjects and demonstrated empirical evidence for their association (Friedel et al. 2014; Gillan et al. 2015).

In normal functioning, habits and goal-directed actions are in equilibrium to allow optimal behavioural performance. Compulsivity arises when this balance becomes disrupted and control becomes biased towards the habitual system, via either an over-strengthening of the habitual system or deficiencies in the goal-directed action system (Gillan et al. 2016b).

1.4.3.1 Contingency degradation as an assay of goal directed actions and habits

Multiple variables are evaluated when an animal makes a goal-directed action. The value of the potential outcome is weighed against the cost entailed by the action, as well as how likely it is that the proposed action will result in the desired outcome. However, this knowledge alone is insufficient to promote the

execution of a particular action; the likelihood of the outcome occurring without the action being performed must also be taken into account (Schultz 2015). Again, this is highly adaptive – there is little point expending energy performing an action if the outcome will occur anyway, "for free". The dichotomy was first formalized in Pavlovian conditioning as the concept of contingency (Rescorla 1967; 1968), and can be defined in an instrumental context as the difference between the probability of reinforcer delivery given a response and the probability of reinforcer delivery in the absence of that response (Hammond 1980).

The subjective value of the outcome and the contingent relationship between the action and the outcome are thus both important facets of goal-directed actions. They can be assessed using outcome revaluation[20] and contingency degradation tests respectively, classic paradigms where behaviour which is altered in response to either challenge is shown to be goal-directed, and that which continues unchanged is known to be habitual. In the former test the value of the outcome is altered, for example by inducing sensory-specific satiety (Colwill and Rescorla 1985b; Rolls 1986; Hetherington and Rolls 1996; Balleine and Dickinson 1998b) or a conditioned aversion to a food reward (Adams and Dickinson 1981a; Colwill and Rescorla 1985b; Colwill and Rescorla 1985a) or by changing the subject's motivational state (Dickinson and Dawson 1987; Dickinson 1989). A re-direction of instrumental behavior consistent with the new outcome value occurs if the behavior is goal-directed in nature (Adams 1982; Colwill 1993; Dickinson and Balleine 1995). In contingency degradation, the contingent relationship between the action and its outcome is weakened by the delivery of noncontingent outcomes. Performance of the action declines if it is goal-directed, an effect which has been shown in rats (Hammond 1980; Dickinson and Charnock 1985; Balleine and Dickinson 1998a), mice (Gourley et al. 2013a; b), marmosets (Jackson et al. 2016) and humans (Chatlosh et al. 1985; Shanks and Dickinson 1991); a similar effect is also seen in human causal judgments (Allan and Jenkins 1980; Wasserman et al. 1983; Chatlosh et al. 1985; Neunaber and Wasserman 1986; Shanks and Dickinson 1988; 1991).

1.4.3.2 Contingency degradation, habits and OCD

The habit hypothesis is a neuropsychological framework that has been theorised to underlie the pathology of OCD (Graybiel and Rauch 2000; Gillan and Robbins 2014). It is thought that deficits in the regulation of goal-directed actions give rise to over-dominance of the habit system which manifests as behavioural compulsions (Gillan et al. 2016c), and that these compulsions then cause the development of obsessions by reverse inference, also termed *post-hoc* rationalisation (Gillan and Sahakian 2015; Kalanthroff et al. 2016). OCD patients were demonstrated to have a greater reliance on habitual strategies, at the expense of goal-directed actions, in both appetitive and aversive contexts (Gillan et al. 2011; 2014, d; Voon et al. 2014).

[20] Outcome revaluation is the term used in preference in this instance to "outcome *de*valuation", a term overwhelming more widespread in its use throughout the literature. Outcome revaluation is the more general term, covering a potential increase or decrease in the value of the outcome, either of which would be suitable to be used to assess whether behaviour is under goal-directed or instrumental control; given goal-directed control of behaviour, for an increase in outcome value responding should increase and for a decrease in outcome value responding should decrease. However, due to the methods commonly employed to change the value of an outcome, outcomes are almost universally decreased in value, thus leading to the preponderance of the term outcome devaluation. Outcome devaluation will be used in this thesis when referring to specific experiments in which it is an appropriate descriptor, and may be used interchangeably with outcome revaluation when discussing the paradigm generally.

The driver of the disrupted balance between habits and goal-directed actions was identified as impaired goal-directed control in subsequent work; OCD patients exhibit deficits in counterfactual thinking[21] between different action-outcome scenarios, and a greater reliance than control subjects on expected value during decision making (Gillan et al. 2014c). In further support of deficient goal-directed action control, there is evidence that OCD patients have impairments in planning, as commonly assayed by the Towers of Hanoi or London tasks. Several groups have reported impairments in these tasks, either in terms of reaction time or performance, in patients (Veale et al. 1996; Purcell et al. 1998a; Cavedini et al. 2001; Cavedini et al. 2010; Nielen and Den Boer 2003; Cavallaro et al. 2003; Heuvel et al. 2005; Chamberlain et al. 2007a; Huyser et al. 2010; Rampacher et al. 2010; Ornstein et al. 2010; Krishna et al. 2011; Tükel et al. 2012; Dittrich and Johansen 2013), their unaffected first-degree relatives (Delorme et al. 2007; Cavedini et al. 2010) and subclinical obsessive-compulsive cohorts (Mataix-Cols et al. 1999b; Mataix-Cols 2003), though there have also been negative findings (Schmidtke et al. 1998; Beers et al. 1999; Watkins et al. 2005; Bannon et al. 2006); varying results have been ascribed to methodological differences (Heuvel et al. 2005).

Evidence for *post-hoc* rationalisation of compulsions to form obsessions hails from the literature on *safety behaviour*s, defined as actions aimed at preventing or minimising a feared outcome (Uijen and Toffolo 2015). Safety behaviours are common in anxiety disorders and have long been theorised to exacerbate such illnesses by removing opportunities for patients to disconfirm the presence or severity of threats (Salkovskis 1991; Rachman et al. 2008). The performance of safety behaviours have been shown to block extinction of fear conditioning and maintain threat expectations, even to stimuli never paired with negative outcomes in healthy individuals (Lovibond et al. 2009; Volders et al. 2012; Engelhard et al. 2015) and to induce doubt of memory and perception (Hout and Kindt 2003; Radomsky et al. 2006; Coles et al. 2006; Boschen and Vuksanovic 2007; Hout et al. 2008), as well as increasing discomfort and the urge to perform further safety behaviours in both healthy individuals and OCD patients (Salkovskis et al. 1997; Salkovskis et al. 2003; Ahern et al. 2015). Finally, intrusive cognitions about threat can be induced in healthy individuals by instructing them to repeatedly perform safety behaviours such as checking (Deacon and Maack 2008; Olatunji et al. 2011; Uijen and Toffolo 2015).

Neuroimaging work has linked the excessive habit formation in OCD patients with reduced grey matter volume (Voon et al. 2014) and hyperactivation of the caudate nucleus during a habitual avoidance task, with greater activity in the region correlating with the experienced urge to perform habits (Gillan et al. 2014a). OCD patients who went on to develop habits in the avoidance task showed a positive coupling between level of activity in the caudate and the subgenual ACC, whereas those that did not, displayed a negative coupling. The medial OFC was also implicated: reduced grey matter volume was associated with habit formation, and increased activation was seen during the habitual avoidance task, though this was not specifically linked to habit development (Voon et al. 2014; Gillan et al. 2014a). The negative results for the differential recruitment of the putamen in the habitual avoidance task were interpreted as support for compulsive behaviour arising in OCD as a result of dysfunctional goal-directed action control rather than an overstrengthened habitual system (Gillan et al. 2014a). OCD patients (and high-scoring individuals

[21] Counterfactual thinking is the "might-have-been" reconstruction of past events (Roese 1997). Upward counterfactual thinking is the consideration of alternate scenarios which give better outcomes than what has actually happened and is known to induce regret and to play an important role in decision making (Loomes and Sugden 1982; Roese 1994).

on measures of obsessive-compulsive symptoms) have also been revealed to display reduced recruitment of fronto-striatal circuitry during planning in the Tower of London task (Heuvel et al. 2005; Heuvel et al. 2011; Braber et al. 2008; Huyser et al. 2010), particularly with respect to the dlPFC (Heuvel et al. 2005; Heuvel et al. 2011; Braber et al. 2008; Huyser et al. 2010), thalamus (Heuvel et al. 2011; Braber et al. 2008) and caudate (Heuvel et al. 2005; Heuvel et al. 2011). In another planning–focused paradigm, the One Touch Stockings of Cambridge test, OCD patients showed impairments, the magnitude of which inversely correlated with strength of functional connectivity between the putamen and the dlPFC (Vaghi et al. 2016).

Furthermore, in a recent symptom provocation avoidance task, OCD patients showed a pattern of neural recruitment consistent with hyper- and hypoactivity in circuitry associated with habitual and goal-directed control respectively: decreased activity in vmPFC, dlPFC and dorsal caudate, and increased activity in the putamen, caudal cingulate, presupplementary and supplementary motor areas, subthalamic nucleus and limbic regions such as amygdala and insular cortex, with the structures causally influencing the circuitry identified as the vmPFC and putamen by effective connectivity analysis (Banca et al. 2015).

There is evidence to suggest that altered contingency learning may be the cause of the goal-directed action deficits in OCD. Though there have been conflicting findings ascribed to differing task parameters, OCD patients have been shown to give estimates of action-outcome contingencies that are at variance with those given by control subjects (Reuven-Magril et al. 2008; Gillan et al. 2014b). These findings would also support an alternate psychological theory whereby OCD patients have a reduced sense of control over life events, and use compulsive behaviours to compensate, thereby imparting an illusory sense of control (Frost et al. 1993; McLaren and Crowe 2003; Moulding and Kyrios 2006; Moulding et al. 2007a; Reuven-Magril et al. 2008).

1.4.3.3 Neuroanatomical substrates of contingency degradation

Several key areas have been implicated in the circuitry of goal-directed actions and habits including the mPFC, OFC and striatum, with much of the work utilising the outcome revaluation and contingency degradation tasks. However, the lack of a definitive homology between these regions in the species investigated, rats, non-human primates and humans, has made it difficult to synthesise the findings. Furthermore, many studies have used paradigms which contained both Pavlovian and instrumental elements, thus obfuscating a precise isolation of the underlying psychological associations (i.e. stimulus- or action-outcome).

The medial prefrontal cortex (mPFC) of rats has been implicated in behavioral sensitivity to contingency degradation. A pre-training lesion of the rat prelimbic cortex (PL) has been shown to induce insensitivity to subsequent contingency degradation (Balleine and Dickinson 1998a). There is disagreement however regarding the sector of primate mPFC to which the rodent PL corresponds (Myers-Schulz and Koenigs 2012). Based on the findings from human neuroimaging studies of contingency learning (Tanaka et al. 2008; Liljeholm et al. 2011), it has been suggested that an anterior part of ventromedial PFC that encroaches on Brodmann area (BA) 10/14 may be equivalent to PL (Balleine and O'Doherty 2010). In

contrast, PL has also been likened to dorsal anterior cingulate cortex (ACC), BA 24, in humans since both regions have been implicated in the regulation of conditioned fear (Milad and Quirk 2012). However, consideration of cytoarchitecture and receptor distribution patterns points to primate perigenual anterior cingulate cortex (pgACC), area 32, as equivalent to PL (Gabbott et al. 2003; Vogt et al. 2013). There is therefore a clear need for translational studies of contingency degradation in non-human primates, such as Jackson et al. 2016, in order to investigate contingency degradation using a species in which the structure and functional organization of the PFC has a greater similarity to humans compared with that of rodents (Uylings and Eden 1991).

Optogenetic perturbation of activity in the neighbouring IL cortex conversely induces goal-directed actions and reduces habitual behaviour (Smith et al. 2012; Smith and Graybiel 2013) as does excitotoxic lesioning (Killcross and Coutureau 2003), inactivation with muscimol (Coutureau and Killcross 2003; Haddon and Killcross 2011), and the infusion of DA, D_1 receptor antagonists or D_2 receptor agonists into the area (Hitchcott et al. 2007; Barker et al. 2013). IL cortex is proposed to mediate an executive level of control of habit selection, coordinating with the DLS where the habit representations are thought to be stored (Smith and Graybiel 2013; Barker et al. 2014). As with the PL, there is currently a lack of consensus on the homologous region to the IL in the primate (Dolan and Dayan 2013).

The orbitofrontal cortex (OFC) is another key region thought to contribute to goal-directed behavior, though the majority of studies which have investigated its role have used outcome revaluation rather than the comparatively lesser-studied paradigm of contingency degradation. The OFC has been shown to be necessary for sensitivity to outcome revaluation in both rodents (Gallagher et al. 1999; Pickens et al. 2003; 2005) and rhesus macaques (Izquierdo et al. 2004; Machado and Bachevalier 2007a; b; Baxter et al. 2009; West et al. 2011; Rhodes and Murray 2013). The critical region in the macaque has been further specified to be lateral rather than medial OFC, as lesions of areas 11 and 13 but not area 14 (delineated according to Carmichael and Price 1995) were found to produce an impairment in outcome devaluation (Rudebeck and Murray 2011). This directly contrasts with results from human functional neuroimaging, in which modulation of medial OFC (area 14/10) activity during devalued but not valued action selection is reported (Gottfried et al. 2003; Valentin et al. 2007), and also with a recent finding by Bradfield et al. 2015 in which the medial OFC of the rat was shown to be necessary for sensitivity to outcome devaluation. The authors found however that the medial OFC was not needed for normal performance in several other tasks, including contingency degradation (but see Gourley et al. 2010), and theorised that the function of the OFC, or at least its medial region, in goal-directed actions may be limited to situations where information about the relationship between actions and their outcomes is not directly observable, and animals must instead use and retrieve knowledge of the outcomes associated with the available actions. At any rate, the Bradfield study is a timely reminder that outcome devaluation and contingency degradation cannot necessarily be used interchangeably as assays of goal-directed action, and that a focus on the specific psychological processes used in particular tasks may reveal information about the contribution of the OFC to different facets of goal-directed action.

In an investigation which did focus directly upon the role of the OFC in contingency degradation, large lesions of ventral and lateral OFC in rats were shown to disrupt behavioral sensitivity to the degradation

of stimulus-outcome contingencies (Ostlund and Balleine 2007). This result tallies with the recent observation that increased activity during goal-directed, as opposed to habitual actions, occurred in lateral OFC projection neurons in mice, and that chemogenetic inactivation or optogenetic activation of the area decreased or increased, respectively, the level of goal-directed behavior (Gremel and Costa 2013).

Regions of the striatum have been shown to be differentially involved in goal-directed actions and habits, with the caudate and putamen (dorsomedial and dorsolateral striatum (DMS and DLS) respectively in rodents) identified as the respective neuronal correlates (Yin and Knowlton 2006; Johnson et al. 2007; Balleine et al. 2007; 2009; White 2009; Ashby et al. 2010). Lesioning or inactivating the posterior DMS (pDMS) in rats or mice induces insensitivity to contingency degradation and outcome devaluation (Yin et al. 2005b; Hilario et al. 2012 but see Torres et al. 2016b), as does the infusion of NMDAR antagonists in the pDMS but not the DLS (Yin et al. 2005a). DMS lesions also impair flexible place learning, with rats instead using inflexible habit-like strategies (Devan et al. 1999; Yin and Knowlton 2004). Conversely, lesions of the DLS enhanced sensitivity to action-outcome contingencies in outcome devaluation and omission training paradigms (Yin et al. 2004; Yin et al. 2006; Hilario et al. 2012) and induced deficits in the performance of other tasks thought to rely heavily upon stimulus-response associations (Reading et al. 1991; Featherstone and McDonald 2004b; a; 2005, b) (but the DMS may encode stimulus-response associations in certain circumstances, see (Featherstone and McDonald 2005a)).

A wealth of rodent electrophysiological data has also supported the roles of the DLS in habit formation. DLS neurons show a distinctive pattern of activity which is reorganised during the learning of habitual tasks to result in "beginning-and-end" or "boundary" signals which bookend action sequences (Burguière et al. 2015), i.e. there is activity in the area antecedent to the behavioural routine and also at the end of a trial, once decision making has been completed but prior to reward delivery (Jog et al. 1999; Barnes et al. 2005; Jin and Costa 2010; Thorn et al. 2010; Smith and Graybiel 2013; Jin et al. 2014). The activity does not change under outcome devaluation (Smith and Graybiel 2013), and increases as training progresses and correlates with task performance (Thorn et al. 2010). The same pattern of activity has also been found in macaques in the PFC and striatum (Fujii and Graybiel 2003; Desrochers et al. 2015). It has been theorised these signals are a result of action chunking that occurs in habit formation, where behavioural routines are stored and, upon presentation of the appropriate stimulus, played back from the beginning to the end signal (Graybiel 1998; 2008). Such boundary signals were not found in another recent electrophysiological investigation however, in which it was instead found that DLS neurons represented contextual and motor information needed for optimal execution of the motor habit, with the authors ascribing the discrepancy to task differences (Rueda-Orozco and Robbe 2015). Finally, in another contrasting result, Stalnaker et al. 2010 showed that neural activity in the DMS and DLS reflect stimulus-response and action-outcome associations to the same extent and therefore argued that the contrasting roles of the area are enacted not through differing informational content but instead via the ways the regions interact with downstream areas.

Lesion, inactivation and electrophysiological investigations in the non-human primate studies implicate the anterior caudate/putamen and posterior putamen as being functionally homologous to the DMS and DLS respectively in rats (Redgrave et al. 2010). Neurons in the caudate nucleus show activity which correlates with movement and is modulated by reward expectancy and delivery (Kawagoe et al. 1998; Hassani et

al. 2001; Lau and Glimcher 2007). Furthermore, muscimol inactivation of the anterior caudate/putamen impaired new sequence learning while inactivation of the posterior putamen impaired the performance of well-learned sequences and vice versa, results which were confirmed by electrophysiological recordings (Miyachi et al. 1997; 2002).

Human neuroimaging data regarding the striatal contribution to goal-directed actions and habits has also generally supported the caudate/goal-directed action and putamen/habit localisations of function. The level of activity in the anterior caudate has been associated with the strength of contingency between actions and outcomes (Tanaka et al. 2008; Liljeholm et al. 2011), as well as merely the perception of a contingent relationship (Tricomi et al. 2004), while the move to habitual control over extensive training was associated with the progressive increase in recruitment of the putamen (Tricomi et al. 2009). Furthermore, decisions made using forward planning or learned through extensive training were linked to anterior caudate or putamen activity respectively (Wunderlich et al. 2012). In an fMRI-computational modelling study, Brovelli et al. 2011 also supported the roles of the caudate and putamen in goal-directed and habitual behaviour respectively, specifically linking activation in the caudate nucleus to monitoring performance and the integration of the resulting performance estimate with an appraisal of the amount of cognitive resources required, and activation in the putamen to the likelihood that stimuli were linked to the correct response. White matter tract strength between the premotor cortex and the posterior putamen, as well as grey matter density of the latter, predict the display of habitual "slips of action" whilst white matter tract strength between the vmPFC and caudate predict goal-directed actions (Wit et al. 2012). Similarly, in fMRI studies of motor sequence learning, increased recruitment of the sensorimotor region of the putamen is seen with extended practice (Doyon et al. 2002; Floyer-Lea and Matthews 2004; Lehéricy et al. 2005; Coynel et al. 2010), though some studies have failed to find differential striatal activation between putatively habitual and control conditions (Jansma et al. 2001; Wu et al. 2004), while conversely the recruitment of the caudate nucleus decreases with practice and the development of automaticity (Floyer-Lea and Matthews 2004; Poldrack et al. 2005). Moreover, in Parkinson's Disease (PD), an illness characterised by striatal dopamine depletion, patients show impairments in tasks designed to elicit the development of habits (Knowlton et al. 1996; Hay et al. 2002), struggle to develop automaticity of movements (Wu and Hallett 2005) and fail to display motor chunking in sequencing tasks (Tremblay et al. 2010). However, in a recent study by Liljeholm et al. 2015, the tail of the caudate and the ventral striatum were the striatal regions associated with behavioural insensitivity to outcome devaluation, not the putamen.

Research into the neuropsychology of OCD, as described so far, is necessary but not sufficient to gain an understanding of the disorder that could translate into therapeutic advances. For that, the underlying pharmacology of the disorder must also be investigated. Neurotransmitter systems that have been implicated in the pathology of OCD include glutamate (Chakrabarty et al. 2005; Pittenger et al. 2006; Bhattacharyya and Chakraborty 2007; Ting and Feng 2008; Wu et al. 2012; Kariuki-Nyuthe et al. 2014), 5-HT (Insel et al. 1985; Barr et al. 1992; Zohar and Kindler 1992; Zohar et al. 2000; Dijk et al. 2010; Abudy et al. 2012) and DA (Goodman et al. 1990; 1992; Denys et al. 2004d; Koo et al. 2010), with studies addressing their involvement using genetics, receptor binding assays, animal modelling and clinical drug response data. The evidence supporting the role of 5-HT and DA in OCD, as is relevant to this thesis, are described in the next section.

1.5 Pharmacology of OCD

1.5.1 Serotonin hypothesis of OCD

There are several lines of evidence which suggest that dysfunction of the serotoninergic system is a key factor in the neuropathogenesis of OCD. The *serotonin hypothesis of OCD* was initially postulated due to the efficacy and consequent biochemical effects of clomipramine in OCD treatment (§1.2.3.5; Thorén et al. 1980a; Flament et al. 1987 but see Insel et al. 1985). An *ex vivo* study in guinea pigs found that electrically-evoked 5-HT release in the OFC was enhanced after eight but not three weeks of paroxetine treatment as a result of desensitisation of the 5-HT autoreceptors, a result which correlates with the time course of SSRI efficacy in OCD (Mansari et al. 1995; Bergqvist et al. 1999). In opposition to these findings however, tryptophan depletion in OCD patients has been found to have no effect on obsessive-compulsive symptoms (Barr et al. 1994; Smeraldi et al. 1996; Berney et al. 2006; Külz et al. 2007).

Another line of enquiry into the role of serotonin in OCD uses neuroimaging with 5-HT receptor-specific ligands. Serotonin transporter (SERT) availability has been shown to be decreased in the thalamus and/or hypothalamus (Stengler-Wenzke et al. 2004a; Hesse et al. 2005; 2011; Reimold et al. 2007; Zitterl et al. 2007; 2008) and in the midbrain and/or brainstem (Stengler-Wenzke et al. 2004a; Hesse et al. 2005; Hasselbalch et al. 2007; Reimold et al. 2007), though there have been negative findings for both areas (Simpson et al. 2003; Van Der Wee et al. 2004; Zitterl et al. 2009; Matsumoto et al. 2010) and a contradictory result (Pogarell et al. 2003). In addition there is sparse evidence for SERT availability changes in a handful of other areas including the OFC (Matsumoto et al. 2010), striatum (Hesse et al. 2011), amygdala (Hesse et al. 2011), insula (Matsumoto et al. 2010) and anterior cingulate (Hesse et al. 2011). Fewer studies have examined the 5-HT_{2A} receptor. There is evidence for decreased 5-HT_{2A} receptor binding in the PFC (Perani et al. 2008) and increased 5-HT_{2A} receptor binding in the bilateral caudate which decreased with successful treatment (Adams et al. 2005), though there have been negative findings for the former result (Adams et al. 2005; Simpson et al. 2011b). A related study found that the 5-HT synthesis capacity of OCD patients was reduced in the right hippocampus and left temporal gyrus, and in male patients only, in the right caudate (Berney et al. 2011).

Genetic association studies that have attempted to link serotoninergic genes to OCD have yielded inconclusive results (Dijk et al. 2010; Nicolini 2010). Some groups have reported an association between OCD, often stratified into patient subgroups, and the SERT gene *SLC6A4* (McDougle et al. 1998; Bengel et al. 1999; Cavallini et al. 2002; Ozaki et al. 2003; Delorme et al. 2005; Perez et al. 2006; Denys et al. 2006; Dickel et al. 2007; Baca-Garcia et al. 2007; Saiz et al. 2008; Cengiz et al. 2015) whilst others have reported negative findings (Billett et al. 1997; Frisch et al. 2000; Di Bella et al. 2002; Chabane et al. 2004; Meira-Lima et al. 2004; Wendland et al. 2006; Tibrewal et al. 2010). A meta-analysis reported that OCD was associated with the SS homozygous genotype but was inversely associated with the LS heterozygous genotype of the 5-HTT-linked polymorphic region (5-HTTLPR) in the promotor region of the gene (Lin 2007), while another meta-analysis only found associations between the subtypes of early-onset OCD and caucasian patients and the L allele (Bloch et al. 2008b). The more recent consideration of a subtype of the

L allele, L_G (containing a guanine substitution) revealed that the polymorphism was much more prevalent in OCD subjects than controls (Hu et al. 2006), a finding confirmed by meta-analysis (Taylor 2013). Furthermore, a relationship was recently demonstrated between *SLC6A4* polymorphism and size of the right OFC in OCD patients and not controls (Atmaca et al. 2011). The 5-HT_{2A} receptor gene may also be involved in the pathology of OCD but again results have been conflicting (Enoch et al. 2001; Walitza et al. 2002; Dickel et al. 2007), though its association has been confirmed in a meta-analysis (Taylor 2013).

Finally, there are a range of serotoninergic animal models of OCD, both pharmacological and genetic, that lend compelling support to the serotonin hypothesis (Joel 2006a; Albelda and Joel 2012a; Albelda and Joel 2012b; Alonso et al. 2015b; Ahmari 2016). In an early pharmacological investigation, Yadin et al. 1991 proposed that 5-HT_{1B} receptor agonist-induced reduction of spontaneous alternation behaviour in rats could model the perseverative and indecisive behaviour of OCD patients, and showed that SSRI treatment had a protective effect on the behavioural disruption, results which have since been validated by other groups (Fernández-Guasti et al. 2003; Seibell et al. 2003; Ulloa et al. 2004). Moreover, the systemic administration of a 5-HT_{1B} receptor agonist in mice has also been found to induce perservative behaviour and task-related deficits seen in OCD, which can be blocked by 5-HT transporter knockout or SSRI treatment (Shanahan et al. 2009; 2011; Woehrle et al. 2013; Ho et al. 2016). The site of action of the OCD-like behaviour-inducing 5-HT_{1B} receptor agonism was localised to the OFC (Shanahan et al. 2011), and was also shown to increase activity in the dorsal striatum (Ho et al. 2016). In mouse genetic studies, both 5-HT_{2C} receptor (Chou-Green et al. 2003) and tryptophan hydroxylase 2 (Angoa-Pérez et al. 2012) knockout mice appear to develop compulsive-like behaviours.

1.5.2 Dopamine and OCD

Evidence for dopaminergic involvement in OCD arises from a range of sources including animal models of compulsivity (Joel 2006a; Boulougouris et al. 2009b; Albelda and Joel 2012a; Albelda and Joel 2012b; D'Angelo et al. 2014; Campos-García Rojas et al. 2015; Alonso et al. 2015b; Szechtman et al. 2016), neuroimaging of the dopaminergic system and DA-related genetics in OCD patients (McDougle et al. 1993; Denys et al. 2004d; Koo et al. 2010), as well the efficacy of dopaminergic anti-psychotic drugs as adjuncts to mainline SSRI treatment (McDougle 1997).

The quinpirole sensitisation model is perhaps the most prominent dopaminergic animal model of OCD. The repeated administration of the $D_{2/3}$receptor agonist quinpirole to the rat induces compulsive "checking" behaviour of objects placed in an open field (Szechtman et al. 1998; 2001; Eilam and Szechtman 2005; Dvorkin et al. 2006), which is sensitive to the OCD therapies of clomipramine administration (Szechtman et al. 1998) and DBS of the subthalamic nucleus (Winter et al. 2008) or nucleus accumbens (Mundt et al. 2009), and also to lesions of the nucleus accumbens or OFC (Dvorkin et al. 2010) or serotoninergic agonist administration (Tucci et al. 2013). It has also been shown that the model results in the lessening of bursting activity in VTA dopamine neurons (Sesia et al. 2013). The model has recently been re-conceptualised as a lever-based observing response task, and it has been demonstrated that the compulsive checking behaviour is sensitive to uncertainty and to the administration of the $D_{2/3}$ receptor antagonist sulpiride (Eagle et al. 2014).

Another relevant rodent model is that of signal attenuation. Rats are initially trained to lever press for food and the presentation of a stimulus, and then undergo a process of attenuation of external feedback for their behaviour in sessions where the stimulus is presented alone, thus degrading the stimulus–food contingency. When subsequently tested under extinction conditions they exhibit compulsive lever pressing behaviour (Joel and Avisar 2001; Joel 2006b; Goltseker et al. 2015). The compulsive lever pressing is ameliorated by SSRIs (Joel and Avisar 2001), enhanced by OFC lesions or inactivation (Joel et al. 2005a; b; Joel and Klavir 2006), blocked by systemic or intra-OFC administration of a 5-HT_{2C} receptor antagonist (Flaisher-Grinberg et al. 2008), and crucially, has been shown to depend upon a phasic decrease in the stimulation of D_1 receptors (Joel and Doljansky 2003).

There are several other rodent models of OCD that incorporate dopaminergic elements. In the reinforced spatial alternation model, treatment with the 5-HT receptor agonist m-chlorophenylpiperazine (mCPP) augments persistent behaviour on a rewarded T-maze alternation task, which can be ameliorated by pretreatment with fluoxetine (Tsaltas et al. 2005), and further augmented by the administration of quinpirole (Kontis et al. 2008). In another model, knockdown of the DA transporter gene in mice has been shown to induce a compulsive behavioural repertoire which includes hyperactivity, perseverative walking in straight lines and "sequential super-stereotypy", i.e. rigid stereotyped chains of actions, of grooming behaviour (Zhuang et al. 2001; Berridge et al. 2005).

Neuroimaging studies have revealed abnormalities in the dopaminergic system in OCD patients. OCD patients have been demonstrated to have reduced striatal D_2 receptor binding (Denys et al. 2004c; Perani et al. 2008 but see Schneier et al. 2008 who found reductions in patients with comorbid generalised social anxiety disorder only) which increases with fluoxetine treatment (Moresco et al. 2007), reduced D1 receptor binding in the striatum and caudate (Olver et al. 2009; 2010), and increased striatal DA transporter binding (Kim et al. 2003b; Van Der Wee et al. 2004; Pogarell et al. 2005 but see Hesse et al. 2005).

1.5.3 Serotoninergic and dopaminergic findings in non-clinical reversal learning research

1.5.3.1 Serotonin and reversal learning

5-HT is of central importance to reversal learning (Robbins and Crockett 2010), as showcased by studies of peripheral 5-HT manipulations. Several studies have used acute tryptophan depletion (ATD), an intervention which induces transient 5-HT depletion in the CNS (Carpenter et al. 1998), in healthy humans to investigate the serotoninergic basis of reversal learning. Early studies reported impairments following ATD (Park et al. 1994; Rogers et al. 1999a; Murphy et al. 2002) while later studies reported no impairment at the group level (Evers et al. 2005; Finger et al. 2007), but an enhanced reversal-related fMRI signal change in the dorsomedial PFC (Evers et al. 2005), or a drug group by genotype interaction whereby volunteers who were homozygous for the L allele in the 5-HTTLPR of the *SLC6A4* gene were less able to use punishment to guide their responding during reversal learning (Finger et al. 2007). Latterly, ATD was shown to improve punishment- but not reward-based reversal learning, purportedly because 5-HT carries a punishment prediction error, and ATD reduced tonic 5-HT levels allowing a greater signal-to-noise ratio for the phasic 5-HT signal (Cools et al. 2008). Results of acute 5-HT depletion in rodents have also

been mixed, with some studies showing impairments (Masaki et al. 2006; Bari et al. 2010) and another no effects (Brigman et al. 2010).

Systemic administration of SSRIs impairs reversal learning in healthy humans (Chamberlain et al. 2006b) but improved reversal learning in rodents when given acutely, in repeated doses, subchronically or chronically (Bari et al. 2010; Brigman et al. 2010; Brown et al. 2012; Barlow et al. 2015), though one study found that acute, low dose administration impaired rats whilst high doses enhanced performance (Bari et al. 2010). A recent study found decreased monoamine oxidase and Tryptophan hydroxylase 2 expression in the dorsal raphe, interpreted as indicative of a general reduction in serotoninergic tone, and increased monoamine oxidase expression in the OFC, interpreted as a compensatory response to the reduced serotoninergic tone, in rats which were highly perseverative during reversal learning (Barlow et al. 2015).

Genetic manipulations have also been used; constitutive loss of SERT has been shown to improve reversal learning in mice (Brigman et al. 2010; Nonkes et al. 2013 but see Homberg et al. 2007), and the improvement is preserved following cocaine withdrawal (Nonkes et al. 2013). The constitutive loss of 5-HT also had no effect on performance (Brigman et al. 2010). Variation in the promotor region (5-HTTLPR) of the serotonin transporter gene *SLC6A4* has also been linked to reversal learning performance; human L homozygotes show increased responsivity to negative feedback as indexed by increased loss-shifting during reversal learning (Ouden et al. 2013). In rhesus monkeys however, results have been mixed. S carriers of the macaque orthologue, rhesus SERT gene-linked polymorphic region (rh5-HTTLPR), of the same gene displayed enhanced reversal learning (Jedema et al. 2010) in one study, but S homozygotes were shown to be impaired in another (Izquierdo et al. 2007). Additionally the TGT haplotype of the regulatory region in the 3′ untranslated region of the rhesus serotonin transporter gene, which is associated with reduced expression of the transporter (Vallender et al. 2008), was associated with improved reversal learning performance (Vallender et al. 2009).

Work has also been done to specify the serotonin receptor subtypes that may contribute to reversal learning. Systemic administration of low and high doses of a 5-HT_3 receptor antagonist were reported to improve and impair respectively reversal learning in marmosets (Domeney et al. 1991), though this result was not replicated in rhesus monkeys (Arnsten et al. 1997). 5-HT_{2C} receptor KO (Nilsson et al. 2012) or 5-HT_{2C} receptor antagonist treatment (Boulougouris et al. 2008; Nilsson et al. 2012 but see Nilsson et al. 2013) improve reversal learning, which is thought to be mediated by a reduction in the influence of previously non-rewarded associations (Nilsson et al. 2012 but see Nilsson et al. 2013). In a more recent study however, 5-HT_{2C} receptor antagonism improved reversal learning in the early phases of the task, but induced an impairment in the latter stages to give an overall decrement (Alsiö et al. 2015). Conversely, 5-HT_{2A} receptor antagonists impair reversal learning (Boulougouris et al. 2008).

There is evidence to suggest that serotonin acts at the level of the OFC to modulate reversal learning. Selective 5-HT depletion of the OFC causes reversal learning impairments in both rats (Lapiz-Bluhm et al. 2009) and marmosets (Clarke et al. 2004; 2005; 2007), and levels of 5-HT and 5-HT markers in the OFC correlate with reversal learning performance in rats (Masaki et al. 2006; Barlow et al. 2015). Furthermore, neurochemical specificity was confirmed when OFC DA depletion in marmosets had no

effect (Clarke et al. 2007)[22]. The intra-OFC infusion of a 5-HT_{2C} receptor antagonist was shown to mediate the same improving effects as its systemic administration (Boulougouris and Robbins 2010; Alsiö et al. 2015), but not the late-stage impairing effect (Alsiö et al. 2015). Additionally, 5-HT_{2A} receptor binding in the area was associated with reduced perseveration and thus improved performance (Barlow et al. 2015), corroborating the results seen with systemic administration of a 5-HT_{2A} antagonist.

1.5.3.2 Dopamine and reversal learning

There is also evidence to suggest that DA levels affect reversal learning (Klanker et al. 2013a). DA, a neurotransmitter that has previously primarily been associated with reward, has recently been reframed as the "flexibility neurotransmitter", with the reasoning that dopamine modulates but is not essential for reward-based learning, and so may be altering reward-based behaviour to achieve behaviour flexibility (Beeler et al. 2014).

Systemic administration of several types of dopaminergic drugs, including D_1-like, D_2 and D_3 receptor agonists, a $D_{2/3}$ receptor antagonist, a DA reuptake inhibitor and amphetamine have all caused reversal learning deficits in experimental animals and humans (Ridley et al. 1981; Gasbarri et al. 1997; Smith et al. 1999; Mehta et al. 2001; Izquierdo et al. 2006b; 2016, b; Lee et al. 2007; Boulougouris et al. 2009a; Herold 2010; Hatalova et al. 2014; Groman et al. 2016), as has the genetic knockout of D_2 receptors in mice (Kruzich and Grandy 2004; Kruzich et al. 2006). Systemic administration of a DA reuptake inhibitor improved performance at low doses and impaired performance at high doses in a serial spatial reversal learning task, though variation in levels of DA, the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), or DA transporter binding in the DMS or VTA had no effect on individual differences in performance (Barlow et al. 2015). Furthermore, when Parkinson's disease (PD) patients receive dopaminergic drug treatment they develop deficits in reversal learning (Swainson et al. 2000; Cools et al. 2001b; Graef et al. 2010; Buelow et al. 2015), thought to be due to the "dopamine overdose effect", a drug-induced elevation of DA levels to an excessive counterproductive height in regions utilising DA for reversal learning (Swainson et al. 2000; Cools et al. 2001b; Chudasama and Robbins 2006). Findings from dietary dopaminergic depletion studies in humans have given mixed results however. Catecholamine, i.e. noradrenaline and DA, depletion induced a reversal learning deficit (Hasler et al. 2009), while the specific reduction of DA synthesis improved punishment- but not reward-based reversal learning in females only (Robinson et al. 2010).

Similarly, investigations of methamphetamine abuse in animals have hinted at the role of DA in reversal learning. Methamphetamine is known to induce long-lasting depletions in DA that are localised to the striatum (Seiden et al. 1976; Wagner et al. 1980; Ricaurte et al. 1980; Woolverton et al. 1989; Daberkow et al. 2008). Its administration to both rats and monkeys induces impairments in reversal learning (Cheng et al. 2007; White et al. 2009; Izquierdo et al. 2010; Groman et al. 2012; Kosheleff et al. 2012; Stolyarova et al. 2014 but see Daberkow et al. 2008), as well as the downregulation of D_2-like receptors (Groman et al. 2012) and DA transporters (Groman et al. 2012; locus specified to be the striatum: Izquierdo et al. 2010; Kosheleff et al. 2012).

[22] This result is in contrast to that of Calaminus and Hauber 2008, who found that the administration of intra-D1 or -D2 receptor antagonists did produce deficits in reversal learning in rodents. The authors ascribed the differences in results to task differences.

The administration of methamphetamine to rats caused the downregulation of striatal DA transporters as well as deficits in reversal learning (Izquierdo et al. 2010). In vervet monkeys, methamphetamine administration induced the downregulation of D_2-like receptors and DA transporters, the former of which correlated with the magnitude of reversal learning impairment shown (Groman et al. 2012).

There is also genetic evidence for the dopaminergic modulation of reversal learning. The catechol-O-methyltransferase (COMT) enzyme is responsible for the degradation of catecholamines such as dopamine in the body and is encoded by the *COMT* gene (Craddock et al. 2006). Individuals homozygous for the Met allele of the the Val^{158}Met polymorphism in *COMT* have reduced rates of COMT activity and thus elevated levels of neural DA, and exhibit impaired performance in tasks of cognitive flexibility including reversal learning (Krugel et al. 2009; Colzato et al. 2010).

The action of dopamine in reversal learning has been localised to the striatum (Cools 2007). Selective DA depletion in the DLS of rats or the vm caudate of marmosets was found to impair reversal learning (O'Neill and Brown 2007; Clarke et al. 2011), a result found to be neurochemically specific as the depletion of 5-HT the marmoset vm caudate had no effect (Clarke et al. 2011). Moreover, intra-NAcc administration of a $D_{2/3}$but not a D_1receptor agonist also impairs reversal learning (Haluk and Floresco 2009). However, genetic inactivation of tyrosine hydroxylase[23] in the dorsal or ventral striatum of mice was not found to have any effect on reversal learning (Darvas and Palmiter 2011). Additionally, several PET studies have linked striatal dopamine to reversal learning; in vervet monkeys D_2-like receptor availability in the striatum was found to negatively correlate with number of trials to reach criterion during reversal (Groman et al. 2011; 2014), while in humans it has been demonstrated that DA synthesis capacity in the striatum, and change in $D_{2/3}$ receptor availability in the post-commissural caudate after methylphenidate administration can predict reversal learning performance (Clatworthy et al. 2009; Cools et al. 2009). Finally, in a recent human fMRI study, $D_{2/3}$ receptor antagonist-induced increases in striatal recruitment were associated with improvement in reward v.s. punishment reversal learning (Van Der Schaaf et al. 2014).

1.6 Summary of background and problem statement

OCD is a widespread neuropsychiatric disease which can affect all types of people, and induces significant suffering and disability. Efficacious treatment options exist, though there are major problems with treatment access, but even those patients that show a response to treatment often fail to achieve full remission from the disorder. The clinical profile of OCD is highly heterogeneous (Spitzer and Sigmund 1997; Lochner and Stein 2003), in terms of onset, course, comorbidity, and most prominently symptomatology, and this heterogeneity likely underlies the variation in findings from neuroimaging studies. However, neuroimaging results have generally converged to pinpoint abnormalities, both structural and functional, in the corticostriatal circuitry, with a particular focus on the OFC and striatum, as well as in related areas such as the ACC and amygdala.

As a disorder of compulsivity, OCD can be conceptualised both in terms of cognitive inflexibility or as an imbalance between goal-directed actions and habits. Reversal learning and contingency degradation are

[23]Tyrosine hydroxylase catalyses the hydroxylation of tyrosine to form L-DOPA, which is the rate-limiting step in dopamine synthesis (Nagatsu 1995; Kaufman 2006; Daubner et al. 2011).

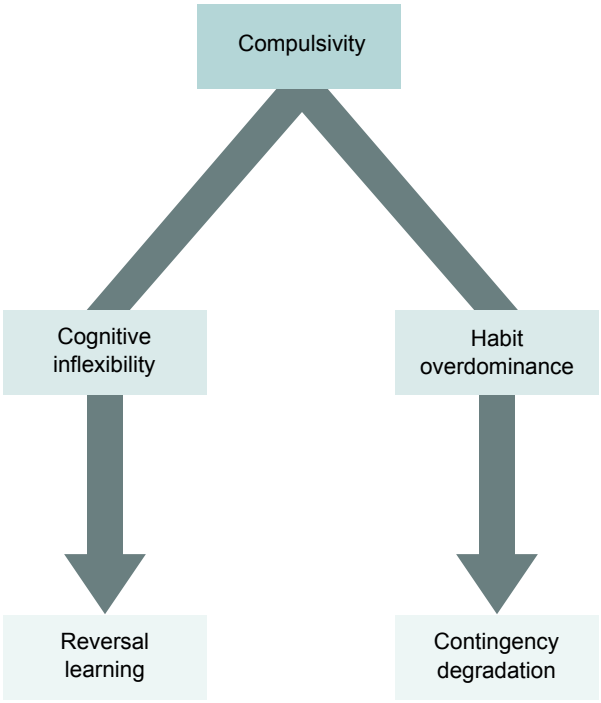

Figure 1.6.1. *Psychological schema of investigation of OCD in this thesis*

classic neuropsychological tests used to assay each of these constructs, as schematized in Figure 1.6.1, and basic research into the neural underpinnings of the paradigms has revealed overlap with those regions identified in OCD neuroimaging, particularly the OFC and striatum. The monoaminergic neurotransmitters serotonin and dopamine are also implicated in both OCD and the neuropsychological paradigms.

The investigations that form part of this thesis have focused on extending the understanding of the anatomical and neurochemical contributions to reversal learning and contingency degradation, with the primary aim of contributing to the basic neuroscience literature surrounding the tasks as well as enhancing our understanding of the neuropsychopharmacology of compulsivity.

In chapter 3, the impact of OFC serotonin on monoamine levels in downstream subcortical structures was determined, and the relevance of the resulting findings to reversal learning subsequently investigated. A panoply of studies have supported the involvement of the OFC and striatum, and in particular the monoamines serotonin and dopamine within those respective regions, in reversal learning. However, there is little empirical evidence of how the two structures and their respective neurotransmitters interact, especially in the context of reversal learning. I thus investigated the effects of unilateral 5-HT depletions in the anterior OFC of the common marmoset and analysed changes in monoamine levels in ipsilateral downstream subcortical structures including different subregions of the striatum, compared with the corresponding areas in the contralateral hemisphere with intact OFC. In a behavioural follow-up experiment, I then performed bilateral serotoninergic depletions in the OFC which would induce the well-characterised reversal learning deficit, but attempted to oppose and counteract the subcortical alterations found in the neurochemical phase of the investigation, with the aim of deducing if the 5-HT

OFC reversal learning deficit was indeed directly caused by OFC dysfunction or by indirect subcortical changes.

In chapter 4, the roles of different regions of the dorsal striatum, the caudate and the putamen, were examined, again in the context of reversal learning. A recent investigation in vervet monkeys found 61% of the individual variation in reversal learning performance of the monkeys could be explained by the interaction of the levels of 5-HT in the OFC and DA in the putamen (Groman et al. 2013). Such evidence for putaminal involvement contrasted with the prior findings of Dr Hannah Clarke in my laboratory which had instead identified the ventromedial caudate as a locus for reversal learning (Clarke et al. 2011). I thus trained a cohort of marmosets on a serial reversal task, the structure of which allowed the use of multiple acute neural manipulations, and separately inactivated the vm caudate and putamen using the $GABA_A$ agonist muscimol, in order to ascertain the precise impact of both interventions.

Finally, in chapter 5, distinct regions of the PFC, the perigenual ACC (pgACC; area 32) and the anterior OFC, were investigated as regards their role in action-outcome contingency degradation. In an investigation recently published by my laboratory (Jackson et al. 2016), excitotoxic lesions of either the pgACC or the OFC were found to induce insensitivity to contingency degradation in marmosets. However, the design of the paradigm did not allow the specification of whether stimulus– or action–outcome associations were being disrupted, nor could a precise orbitofrontal locus be determined as the OFC lesions incorporated parts of the lateral and medial OFC. I thus developed a novel contingency degradation paradigm which enabled the study of acute pharmacological manipulations in both brain regions and was more suited to delineate between stimulus– and action–outcome associations. The pgACC and OFC were temporarily inactivated using muscimol to further clarify the contributions of both areas to sensitivity to contingency degradation.

2 General Methods

Preface to methods

I have chosen to include an unprecedented level of detail concerning the husbandry and welfare of the animals involved in my experiments. The welfare of the animals under our care was paramount to myself and the other members of my lab, with researchers and technical staff alike working to minimise suffering during experimental procedures and to ensure optimal living conditions for happy and healthy monkeys. Common marmosets are highly intelligent with complex environmental, behavioural and social needs, and thus necessitate much effort, care and experience to maintain properly in a laboratory environment. High welfare standards were important not only due to our ethical obligation to protect their physiological and psychological well-being (Novak and Suomi 1988; Crockett 1999), but also to gain reliable data and produce the best quality neuroscience, as the negative impact of stress and substandard care on scientific output from animal research, particularly when studying cognition, is now widely recognised (Poole 1997; Moberg 1999; Garner 2005). However, whilst it is clear that husbandry and welfare have an important bearing on my experiments, and must be reported to ensure replicability (Smith et al. 1997), the involvement is indirect, and thus the majority of the information has been provided in extensive appendices which are cross-referenced in this chapter and the individual methods sections of the experimental chapters (§3.2, 4.2, 5.2). The reporting fully complies with the Animals in Research: Reporting *In Vivo* Experiments (ARRIVE) guidelines produced by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (Kilkenny et al. 2010).

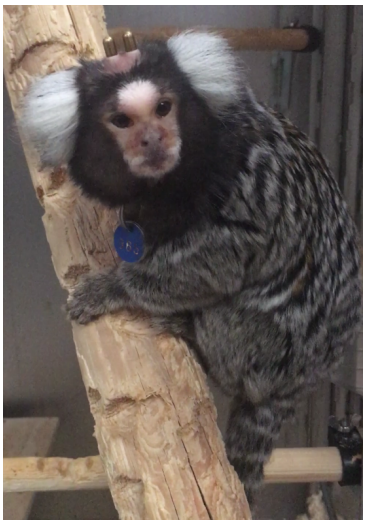

Figure 2.0.1. *Subject 2c climbing on a pole in homecage.*

Table 2.1. *Overview of studies and subject numbers.*

Study	Marmoset	Sex
Neurochemical interactions between OFC and subcortical structures and their relation to cognitive flexibility as assessed by reversal learning	Subject 1a	Male
	Subject 1b	Male
	Subject 1c	Male
	Subject 1d	Female
	Subject 1e	Male
	Subject 1f	Male
	Subject 1g	Male
	Subject 1h	Male
	Subject 1i	Male
Parsing the differential contribution of primate striatal regions to serial reversal learning	Subject 2a	Male
	Subject 2b	Male
	Subject 2c	Male
	Subject 2d	Male
The role of OFC, area 32 and the caudate in goal-directed actions as assessed by contingency degradation	Subject 3a	Female
	Subject 3b	Male
	Subject 3c	Female
	Subject 3d	Female
	Subject 3e	Female

2.1 Subjects, housing and feeding

Eighteen experimentally naïve common marmosets (*Callithrix jacchus*; five female and thirteen male), bred on site in a conventional barrier facility in the University of Cambridge Marmoset Breeding Colony and housed in pairs in custom-made housing (Tecniplast UK Ltd., Kettering, UK), were the subjects of the experiments described in this thesis (Table 2.1). Rooms were maintained at 24°C and 55% relative humidity and were gradually illuminated from 7.00 to 7.30am and dimmed from 7.00 to 7.30pm, following a 12 hour light/dark cycle with dawn and dusk. Males had received a vasectomy to prevent any pregnancies in their female partners. Marmosets received a nutritionally complete diet which consisted of sandwiches, fruit (Hilary's Wholesale Ltd.; Cambridge, UK) and rusk (Farley's Rusk; H.J. Heinz Foods UK Ltd.; Middlesex, UK) at the weekend, and a restricted but calorifically equivalent diet of pellets and fruits and vegetables during the week (§B.2). From Monday to Friday, access to water was restricted for 22 hours out of every 24, with *ad libitum* access for the remaining two hours after behavioural testing, and *ad libitum* access over the weekend. The housing contained a range of environmental enrichment aids including ropes and rope ladders, and marmosets were given occasional treats after testing. Marmosets were weighed on a weekly basis and their welfare monitored by the researcher in conjunction with the NACWO, NVS and the Senior Marmoset Technician and her team (§B.3). All procedures were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986 as amended in 2012, under project licences 80/2225 and 70/7618. In addition, the University of Cambridge Animal Welfare and Ethical Review Board provided ethical approval of the project licence and its amendments, as well as individual studies and procedures via delegation of authorisation to the Named Animal Care and Welfare Officer (NACWO) for individual study plans.

2.2 Testing apparatus

All marmosets were trained to enter a Perspex carrying box (made in house; University of Cambridge Engineering Department). The marmosets who were the focus of the neurochemical investigation in Chapter 3 (§3.2) were not exposed to any other testing apparatus and received no further behavioural training; all others were exposed to the testing apparatus and received preliminary behavioural training (§2.3) and task-specific training (§4.2.1 or 5.2.1). Thus once the latter group of marmosets were inside the carrying box they were transported to a darkened testing room, the carrying box slotted into the metal frame of the touchscreen chamber (Biotronix; Cambridge, UK) and the door removed. The touchscreen chamber comprised a custom-made sound-attenuated box containing a touch-sensitive computer monitor or "touchscreen" (Campden Instruments, Loughborough, UK). Once the door was removed the touchscreen was revealed to the marmoset, and they could reach through a vertical array of metal bars in order to manipulate it. A centrally placed licking spout, containing four tubes connected to separate pumps (Autoclude, Essex, UK), allowed the delivery of up to four liquid reinforcers. Only three reinforcers were used in these experiments however: cooled banana milkshake (Nesquik Banana; Nestlé UK Ltd; York, UK), and strawberry (Ribena Strawberry Squash; Lucozade Ribena Suntory Ltd., Uxbridge, UK) and blackcurrant juice drinks (Ribena Blackcurrant Squash; Lucozade Ribena Suntory Ltd.). Licking was detected by the interruption of an infrared photobeam situated at the mouth of the licking spout. A speaker at the back of the chamber played the sounds used in the experiments: a birdsong recording which acted as a cue to collect reward or a mildly aversive loud noise (~100 dB) used to signal incorrect choices. Stimulus presentation upon the touchscreen, the speaker and the reinforcer pumps were controlled by modules within the MonkeyCantab program (R.N. Cardinal) using the Whisker control system (Cardinal and Aitken 2010). All experiments were monitored in real-time by video cameras mounted to the roof of the touchscreen chamber.

2.3 Preliminary behavioural training

Marmosets were trained to enter the carrying box using positive reinforcement, namely marshmallow reward. They were acclimatised to the carrying box, and then acclimatised to the touchscreen chamber. They were familiarised with banana milkshake in the homecage, and then fed banana milkshake by hand from a syringe in the touchscreen chamber. They were trained to take milkshake from the licking spout by moving the syringe close to the licking spout. Marmosets were then gradually trained, in a manner first described in Roberts et al. 1988, to respond on the touchscreen for banana milkshake. Marmosets were presented with a large green horizontal bar stimulus (Figure 2.3.1A) which when touched caused the onset of eight seconds of banana milkshake delivery from the licking spout and the playback of an auditory cue of a recording of birdsong. Birdsong was always played when milkshake was delivered so that it came to cue reward delivery. Pieces of marshmallow were affixed to the touchscreen on top of the green bar stimulus, such that when the marmosets reached for the marshmallow they touched the green bar and thus milkshake was delivered. Over time they came to associate touching the green bar with milkshake reward, and thus the size and number of pieces of marshmallow was reduced until marmosets were touching in the absence of marshmallow entirely. Furthermore, instead of automatic milkshake delivery upon

touching the stimulus, marmosets were moved to a "lick contingent" condition where upon touching the stimulus birdsong would be played to cue reward *availability,* and milkshake delivery would begin when the marmoset began to lick at the licking spout, as detected by the interruption of the infrared photobeam. Thus touching the stimulus induced eight seconds of milkshake availability, as signalled by the birdsong cue. Following the conclusion of the milkshake availability, there was a one second intertrial interval (ITI) in which the houselight was extinguished and the stimulus disappeared from the touchscreen.

Once marmosets were reliably performing at least thirty or so responses to the bar stimulus, they were moved on to a smaller central square stimulus (Figure 2.3.1B), and once showing equivalent performance on the central square progressed to responding to two square stimuli that appeared on either the left or right side of the screen in a pseudorandom order, a stage known as "two ran" within the MonkeyCantab program. Figure 2.3.1C shows the position of the two squares, but only one square was ever presented at any point. Marmosets were then moved from an eight second reward availability period and one second ITI to six seconds of reward with a two second ITI and then finally to five seconds of reward and a three second ITI. Once marmosets were again reliably performing thirty or so responses under two ran they were moved to one of the further training protocols specific to each of the different touchscreen paradigms described in the respective experimental chapters (§4.2.1 or 5.2.1). Marmosets were tested once daily on Monday to Friday and were not tested at the weekend, and all sessions were twenty minutes long, unless otherwise specified.

2.4 Surgical Procedures

2.4.1 Pre-surgical preparations

Marmosets were weighed the day before and on the day of surgery. If either of those weight measurements had decreased relative to their weight the previous week by 5% or more surgery was postponed. Marmosets were not fed for at least 12 hours prior to surgery to minimise the chance of vomiting when recovering from the anaesthetic. All surgical tools, drapes and consumables were autoclaved (Elara D tabletop autoclave; Tuttnauer Europe B.V., Breda, The Netherlands) in advance of surgery to allow an aseptic field to be created, in line with the Laboratory Animal Science Association's guidelines on aseptic surgery (Laboratory Animal Science Association 2010). All surfaces in the operating theatre and in the pre-operating area were disinfected and wiped down, as was the stereotax.

On the morning of surgery, marmosets were divided into the top right hand quadrant of their homecage, caught by hand using handling gloves (Welder Blue HR Gloves; Honeywell Safety Products Ltd., Basingstoke, UK), and transported to the pre-surgical area. They were premedicated using 0.1 ml of 100 mg/ml ketamine hydrochloride solution (Vetelar; Amersham Biosciences and Upjohn, Crawley, UK) i.m., and placed in an incubator (Figure 2.4.1D; Vetario S20 Intensive Care Unit; Brinsea Products Ltd., Somerset, UK) for approximately five minutes until the ketamine had taken effect and the animal was semi-conscious (for further information see §B.3.2). Marmosets can become hypothermic when under anaesthetic (Unwin 2005), and thus were then placed on a heat mat (unknown manufacturer) to maintain core body

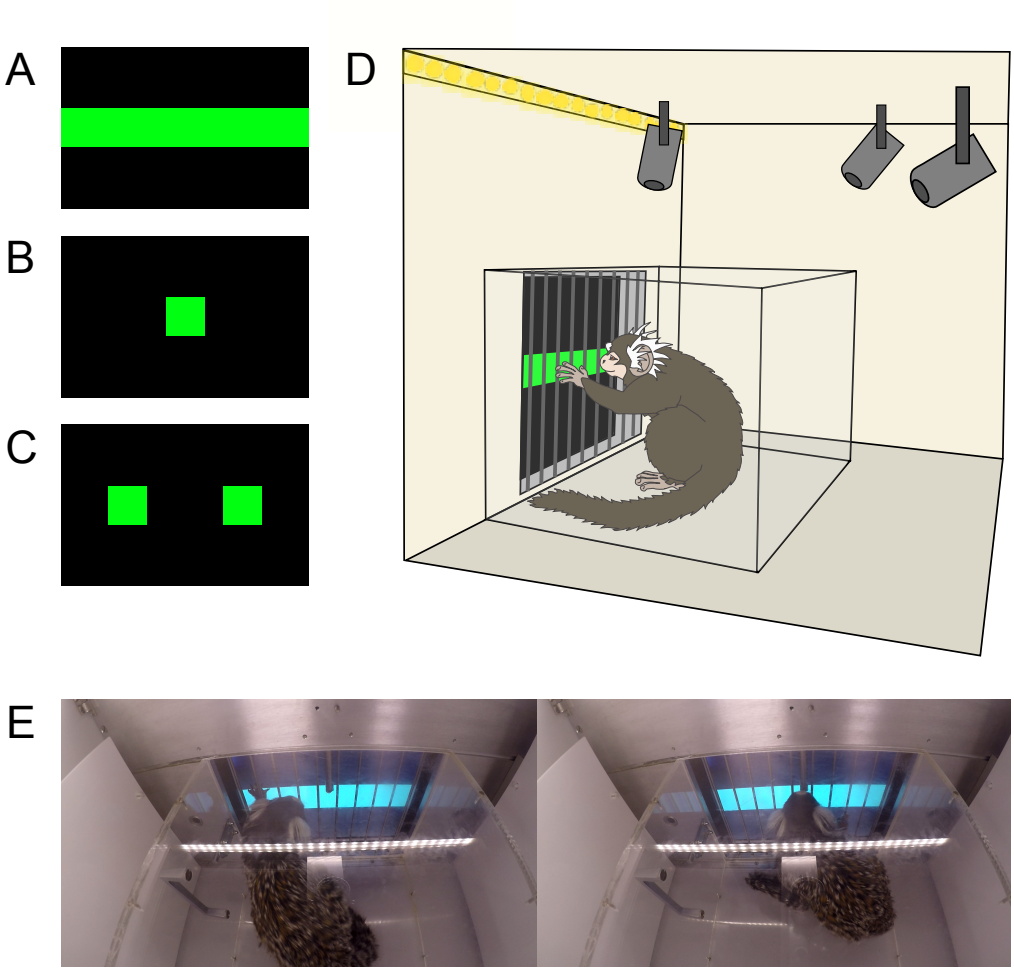

Figure 2.3.1. *Stimuli used in the preliminary touchscreen training. Marmosets progressed through the stimuli shown from A to B to C, and were moved from stage to stage when reliably performing 30 or more responses. D. Schematic of a marmoset in the touchscreen chamber responding to the green bar. E. Subject 3e touching the green bar and receiving milkshake reward.*

temperature with swabs placed beneath the genital area to protect them from the risk of burning. Their hair was shaved using an electric hair clipper (Figure 2.4.1A; Contura Shaver; VetTech Solutions Ltd., Cheshire, UK); their heads were shaved to permit the making of the surgical incision, and also the backs of their and hands and feet shaved to permit the monitoring of vital signs. Marmosets were given 0.03 ml of 50mg/ml carprofen solution (Carprieve; Pfizer, Kent, UK) s.c. as a prophylactic analgesic.

2.4.2 Induction and maintenance of anaesthesia

Anaesthesia was induced by the administration of a mixture of vaporised isofluorane (Novartis Animal Health, Herts, UK) and O_2, controlled using a specialised anaesthetic machine (Compact Anaesthesia Systems; VetTech Solutions Ltd), for further information see §B.3.2. Initially isofluorane was delivered via a facemask with a flow rate of 4% isofluorane in 0.7 l/min O_2 until the marmoset was unconscious with a reduced pulse rate and lack of muscle tension. At this point the marmoset was intubated and isofluorane delivered with a flow rate of 2.5% isoflurane in 0.3 l/min O_2. To intubate the marmosets one researcher would hold the head by the cheekbones, such that the lower jaw hung down of its own accord, while hooking a fingernail underneath the right incisor and gently pulling upwards. Another researcher, or the NACWO, would then pull down on the lower jaw and maintain gentle pressure with one hand, whilst pulling the tongue forward, clearing the mouth of excess saliva with a cotton bud and applying a topical anaesthetic to the back of the throat (Intubeaze 20 mg/ml lidocaine hydrochloride spray; Dechra Veterinary Products Ltd., Shropshire, UK). The second researcher then manoeuvered an intubation tube past the epiglottis, allowing it to slide down the throat. The tubing was connected to the rest of the setup, and the correct positioning of the intubation tube was confirmed by the sight of breathing movements inflating and deflating an attached balloon.

Pulse-rate, O_2 saturation, respiration rate and CO_2 saturation were all monitored by pulse-oximetry and capnography (Figure 2.4.2; Microcap Handheld Capnograph; Oridion Capnography Inc., Massachusetts, USA); core body temperature was monitored by a rectal thermometer (Figure 2.4.1B; MicroTherma 2T digital thermometer; ThermoWorks, Utah, USA) which was covered with a disposable lubricated plastic sheath (Temperature Probe Cover (Pre-lubricated); SA Instruments Inc., New York, USA) for the purposes of hygiene. The percentage of isofluorane in the isofluorane/O_2 mixture and the heat mat temperature were modulated during surgery in response to changes in vital signs, and 0.1ml of warmed saline s.c. was given every 90 minutes to prevent dehydration of the animal and the hind legs and body were turned every hour to stimulate blood flow.

2.4.3 Stereotaxic surgical technique

Following intubation, the marmoset was placed in a stereotaxic frame which was specially modified to fit the species (David Kopf Instruments; California, US). The head was secured in place by the positioning of ear, eye and mouth bars. The eye bars were positioned in the supraorbital foramen of the eye sockets and the mouth bar against the roof of the mouth. Ophthalmic ointment (Lacri-lube; Allergan Inc., California, USA) was applied to the eyes to prevent dryness or irritation after surgery, and the surgical lamp (Brandon

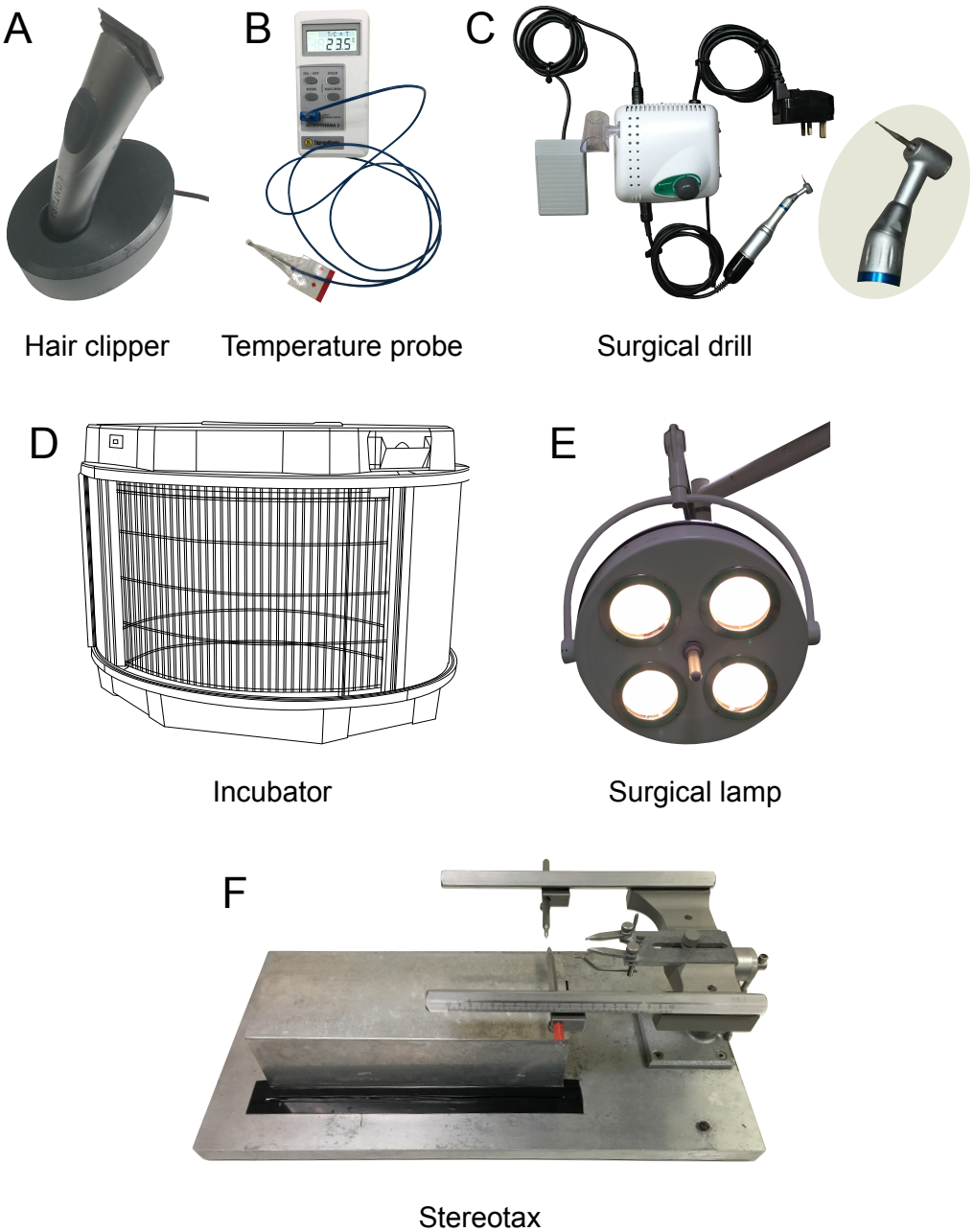

Figure 2.4.1. *Surgical Apparatus. A. Electric hair clipper. B. Rectal thermometer with plastic sheath covering probe. C. Surgical drill. D. Incubator. E. Surgical lamp. F. Stereotax.*

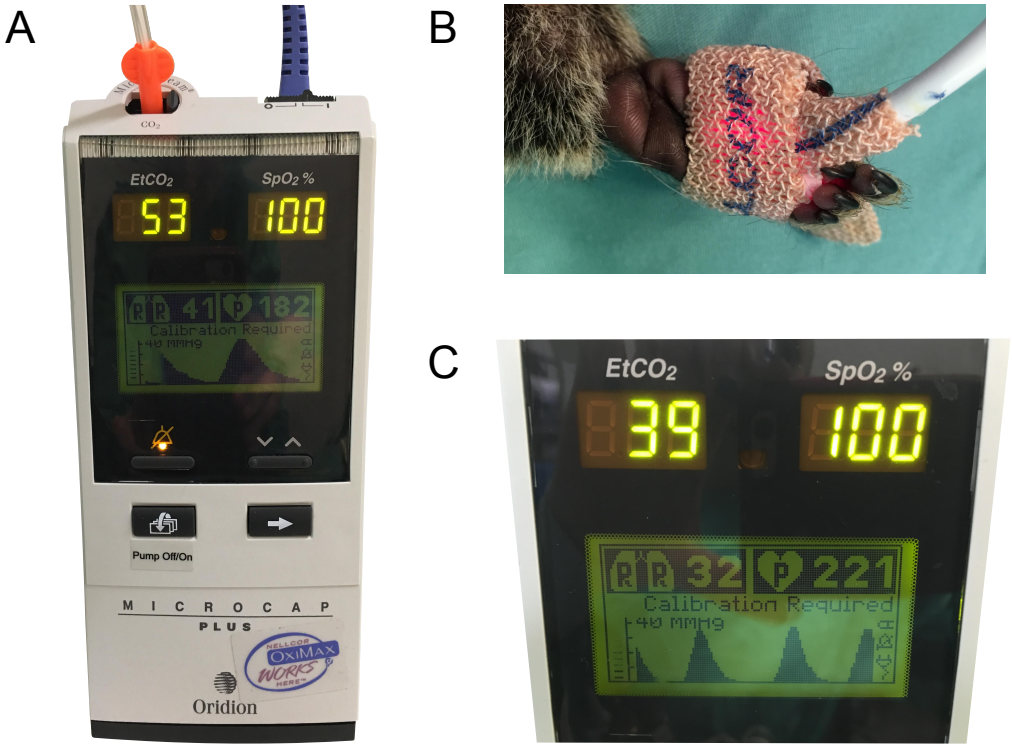

Figure 2.4.2. *Anaesthetic monitoring equipment. A. Capnograph/pulse oximeter, showing clockwise from top left: expired CO_2 partial pressure ($EtCO_2$), oxygen saturation (SpO_2 %), pulse rate, profile of breathing and respiration rate. The tube with orange connector seen on the top left of the photograph samples gases from inside the intubation tube which is not shown here. B. Pulse oximetry sensor applied to hand of marmoset during surgery. C. Close-up view of a typical capnograph readout.*

Medical; Leeds, UK) was positioned above the marmoset so as to illuminate the cranial area, and to shine on the body of the marmoset to help maintain their bodily temperature.

Bactericidal povidone-iodine surgical scrub (Vetasept; Animalcare Ltd., York, UK) was wiped over the head using a cotton swab and a sterile polythene operating cover (Buster Sterile Op Cover; VetTech Solutions Ltd.) placed over the body of the marmoset and drawn up to the top of the neck. An antimicrobial incise drape (Ioban 2 Antimicrobial Incise Drape; 3M, Minnesota, USA) was then placed over the head. An incision was made down the midline, and muscle on the lateral edges pushed back if necessary to expose the skull. A metal tissue spreader was inserted to keep the field open, and pieces of swab wetted with saline were laid underneath the skin to prevent it from drying out.

The interaural line, as identified by the ear bars, was used as the anteroposterior (AP) zero co-ordinate (positive in the anterior direction), whilst the superior sagittal sinus at AP 17.5 was used as the lateromedial (LM) zero coordinate, with all co-ordinates given in mm. A dental drill (Figure 2.4.1C; Dental Unit Polisher/Drill Unit II; Eickemeyer, Tuttlingen, Germany) with attached burr (Ash Steel Burs; Dentsply Ash Instruments, Surrey, UK) was used to remove a small amount of skull at AP +17.5, so that the LM zero co-ordinate could be measured.

2.4.3.1 Standardisation of stereotaxic co-ordinates

Marmosets in the colony have been found to exhibit considerable variation in the size of the cerebrum, and thus an adjustment procedure known as a "depth check", first described in Dias et al. 1997, was used to tailor the stereotaxic co-ordinates to each individual marmoset. At a specified co-ordinate (AP 17.5, LM -1), the thickness of the brain tissue, i.e. the depth from the dorsal to the ventral surface, was determined, and all AP co-ordinates were standardised according to this measurement. After making a craniotomy with the dental drill, a fine probe (Smooth Dental Broach; Micro-Mega, Besancon, France) was lowered using a stereotaxic arm at the designated co-ordinates, and stereotaxic readings taken when the probe touched the surface of the cortex and again at the base of the skull. The point at which the probe reached either criterion was judged to be at the first introduction of a very slight deformation of the thin flexible probe; the surgeon lowered the probe very slowly and monitored it via a microscope (S5 Opmi-MD microscope; Carl Zeiss Ltd., Cambridge, UK) to be able to accurately determine when the deformation took place. If the thickness of the brain tissue was within the range 5.8 - 6.8mm no adjustments were made to the co-ordinates, but if the depth fell outside of that range the measurement process was repeated at 0.5mm intervals along the AP axis (in the anterior direction if the depth was >6.8mm, and in the posterior if the depth was <5.8mm) until the measurement taken did fall within the required range. At that point, the total deviation from the starting co-ordinates was taken as the amount by which all further surgical co-ordinates should be altered with respect to the AP axis. For example, if a movement 0.5mm in the anterior direction had to be made to obtain a depth in the range 5.8 - 6.8mm, all surgical target co-ordinates would be moved 0.5mm in the anterior direction. Only one depth check was required per animal, and thus for subjects which underwent multiple surgeries a depth check was performed in the initial surgery, and the resulting standardisation applied in subsequent surgeries without the need to perform the depth check anew.

2.4.3.2 Cannulation surgery

After completion of the depth check, the guide cannulae (Plastics One, Virginia, USA) were implanted at the newly adjusted co-ordinates. Firstly, an array of steel skull screws (Plastics One) were manually fixed into place across the skull surface using a small hand screwdriver (Drill bit and drill holder; Plastics One). These stabilised the skull and aided the adhesion of the dental cement which was to keep the guide cannulae in place. Small holes were then drilled in the skull at the appropriate locations and a needle was used to pierce the dura. An adhesive (Super-Bond C&B; Sun Medical Co. Ltd., Shiga, Japan) was applied to the surface of the skull using a brush, with care taken not to let the adhesive enter the craniotomies. The guide cannulae were lowered using a stereotaxic arm to the appropriate depth, either vertically or at an angle relative to the AP or LM axes. The point at which the guide cannulae first touched the cortex, and the point at which they could be lowered no further, were measured. Dental cement was applied to the surrounds of the guide cannulae to fix them in place, with care taken to mould the dental cement to form a smooth surface, as rough edges could irritate the skin, and would be more difficult to clean and hence increase the likelihood of infection. The dental cement was allowed to dry fully and dummy injectors (Plastics One) of the appropriate length were inserted into the guide cannulae, followed by protective plastic or metal caps being screwed on top (for some brain regions caps and dummy injectors were integrated). Any plastic caps were susceptible to potentially damaging chewing by homecage partners and so were coated with an unpleasant-tasting substance in order to discourage this (Stop 'n Grow; The Mentholatum Co. Ltd., Glasgow, UK). Descriptions of the stereotaxic co-ordinates and angular positioning used to cannulate the brain regions that were the focus of the experimental studies are given in §4.2.2, and 5.2.3 respectively. Cannulation sites were regularly cleaned to prevent infection (§B.6).

2.4.4 Post-operative care

The skin of the scalp was cleaned and if necessary the edges debrided to allow better apposition of the tissue. The wound was sutured using an absorbable sterile suture (Coated VICRYL® (polyglactin 910) Suture; Ethicon, Puerto Rico, USA), with particular care taken of the tension put on the skin surrounding any cannulae. Following completion of the suturing, the anesthetic was switched off and the marmoset allowed to come round, during which time they were given 0.2 ml dexamethasone phosphate i.m., 0.1ml per hind leg, to prevent tissue inflammation. A "liquid plaster" (Germolene New Skin; Perrigo, Devon, UK) was applied to the line of sutures. Marmosets were taken out of the stereotactic frame, de-intubated and the rectal thermometer removed. They were given oral O_2 for a few minutes, whilst vital signs were closely monitored, until they could maintain O_2 saturation levels unaided. They were placed in the incubator to recover from the anesthesia, where they were kept under frequent observation, and water and food were introduced over the course of 1-2 hours. In the vast majority of cases the marmosets were taken back to their homecage within two hours when the researcher was satisfied they were sufficiently recovered. In the event that the marmoset had not recovered sufficiently by 7.30pm, they were kept in the incubator overnight and returned home early the next morning. Observation of the marmoset continued until they were deemed to have achieved a level of recovery where they could be left safely. The analgesic meloxicam, 0.1 ml of a 1.5 mg/ml oral suspension (Metacam; Boehringer Ingelheim, Germany), was given every 24

hours for a minimum of three days postoperatively for further pain relief, and was extended if required in consultation with the NACWO and Named Veterinary Surgeon (NVS). Marmosets were taken off water restriction and given extra food for a week post-operatively to allow for a full recovery. All surgical instruments were cleaned in warm water with instrument cleaner (Surgical Instrument Cleaner, Animalcare Ltd.) and autoclaved.

2.5 Intra-cerebral drug infusion

Once cannulae had been implanted (§2.4.3.2), infusions could be made to the target areas using the appropriate length injector (Plastics One). For a given brain region the target depth co-ordinate would be the same between marmosets but inter-individual variation in brain and skull size meant that the distance of that target co-ordinate from the surface of the skull, upon which the pedestal of the guide cannula rested, varied slightly between marmosets. To compensate, injectors of differing lengths were used. By design, the guide cannulae terminated immediately above the target area (to prevent any damage by cannula tract to the region of interest itself), and injectors slightly longer than the length of the guide cannulae were used such that the injector protruded from the end of the guide cannula when fully inserted into the target region. The amount by which the injectors were longer than the guide cannulae was varied between 0.5 and 2mm according the measurements of each marmoset.

2.5.1 Infusion procedures

Infusion procedures were standardised in the laboratory and were first described in Clarke et al. 2015. All infusions were carried out in a room separate from the marmoset home rooms. Injectors and tubing were sterile and their setup put together atop a sterile drape (Figure 2.5.1A). Sterile swabs were placed on parts of the infusion pump so that the researcher could operate the pump during the infusion, outside of the sterile field, without compromising sterility. Hamilton syringes (Figure 2.5.1D; Sigma-Aldrich, Missouri, USA) were loaded with saline (sodium chloride 0.9% w/v; Hameln Pharmaceuticals Ltd., Gloucester, UK) and placed in the frame of an infusion pump (Figure 2.5.1C; Kd Scientific, Massachusetts, USA) such that their plungers could be depressed by the forward movement of the pump. Placement was always symmetrical about the centre of the pump to ensure accurate movement. PFTE tubing (inner diameter 0.3mm, VWR International Ltd, UK) was used to connect the Hamilton syringes to injectors, with solva tubing (inner diameter 0.38mm, Pulse Instrumentation, Wisconsin, USA) used to bridge the connections between the PFTE tubing and the other components. A solva tubing bridge, length of PFTE tubing, solva tubing bridge and injector were connected and loaded with saline by syringe before being connected to the Hamilton syringe. The plunger of the Hamilton syringe was manually depressed and then pulled back by a small increment while the injector was held in the air. Thus a small amount of air was loaded into the tubing, and when the injectors were subsequently placed in eppendorf of the drug or saline solutions and the plungers pulled fully back, a small bubble (~2mm) was present in the tubing separating the saline filling the body of the tubing and the drug/saline solution filling the very end. The ends of the bubble were marked using pen and its movement used to check the setup was working (Figure 2.5.1E).

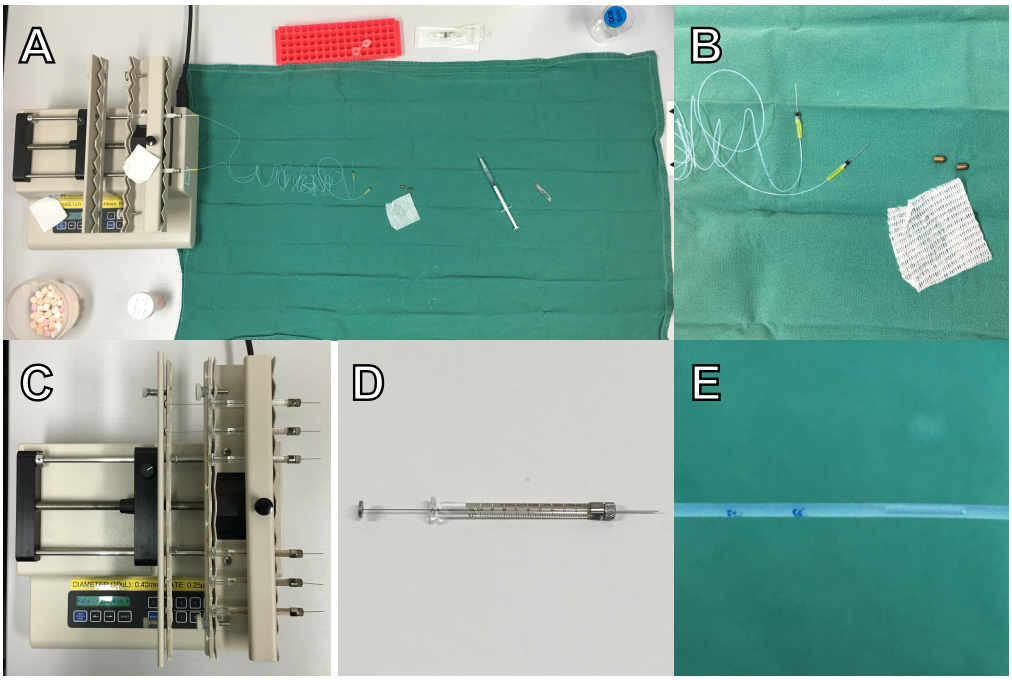

Figure 2.5.1. *Intra-cerebral infusions apparatus. A. Infusion setup. The drape formed a sterile field and all items placed upon it were sterile. Infusion pump is visible on left, loaded with Hamilton syringes which were connected to tubing and injectors. Sterile swabs were used for manipulating the infusion pump to maintain sterility. Shown on drape: injectors and tubing, fresh dummy injectors and caps to be put on the marmoset at the completion of the procedure, a syringe of saline used to load the tubing with saline, scalpel blade used to trim edges of PFTE tubing for easier insertion into solva tubing. Shown surrounding drape: Eppendorfs of drug and saline solutions in an Eppendorf holder. Syringe to replenish saline eppendorf. Ethanol used to clean Hamilton syringes. Whole (large open pot) and chopped pieces of marshmallow (small closed pot). B. Close up view of injectors connected to PFTE tubing via solva tubing and dummy injectors and caps. Dummy injectors are shown threaded through a swab as this is how they were processed for autoclaving. C. Infusion pump with six Hamilton syringes. D. Hamilton syringe. E. Small bubble loaded into tubing has moved from its initial pen markings along the tube, indicating the solution has moved into the caudate and the infusion has been successful.*

Marmosets were divided into the top right hand quadrant of their homecage and caught by hand using handling gloves by another researcher assisting the experimenter. The marmoset was then transferred from the handling gloves to be held with "bare" hands (thin disposable nitrile gloves were worn for hygiene purposes), with the thumb and middle fingers underneath the arms and the index finger sitting on the shoulder. This method of holding was found to be secure yet very comfortable for the marmosets and they rapidly habituated to being held. "Mock infusions" where the marmoset was caught, taken to the infusion room and held whilst the pump was running, were carried out to ensure the marmosets were habituated to the whole infusion process before the first infusions were carried out.

After the infusion apparatus had been set up, the marmoset was caught and held in the manner described. The caps and dummy injectors were removed and the site cleaned with a 70% alcohol wipe. The injectors were inserted into the guide cannulae while the assistant gently held the head of the marmoset if necessary (Figure 2.5.2A, B). Depending on the concentration of the drug solution being infused, the pump was run at a rate of 0.25 or 0.5µl/min for two minutes, giving a total infusion volume of either 0.5 or 1µl. Injectors were left *in situ* for a further minute to allow the diffusion of the infused solution into the brain. During the procedure the marmosets were held loosely and fed chopped pieces of marshmallow (Figure 2.5.2). The injectors were then removed and fresh dummy injectors and caps replaced (Figure 2.5.2F). The marmoset was returned to the homecage and cage dividers removed. Used dummy injectors and caps were cleaned with sonication and autoclaved for re-use. All drugs were dissolved in either distilled water or saline, aliquoted out and stored in a -20°C freezer until needed, at which point an aliquot was removed and allowed to defrost. The defrosted drug solution was vortexed and diluted down with fresh saline if necessary. All drug solutions were used within three months of being made up.

2.6 Euthanasia and histological analysis

All marmosets were euthanased with injection of sodium pentobarbital (Dolethal 1 ml of 200mg/ml solution; Vetoquinol UK Ltd., Buckingham, UK) i.v. (femoral vein). Marmosets were injected and laid on a fleece until their heart was confirmed to have stopped beating with a stethoscope. They were then taken to the post-mortem room, decapitated, and their brains removed. The brains that were to be analysed by reversed-phase high-performance liquid chromatography with electrochemical detection (HPLC-ED), belonging to a subset of the animals that formed study one, were subject to a localised dissection (§3.2.2). All other brains were cannulated and the aim at post-mortem was thus to confirm that the cannula placement was in the regions targeted. Cannulae and dental cement were removed from the brain, with care taken to create as little damage to to the cannulae tracts as possible. The brains were placed in 4% paraformaldehyde solution overnight before being transferred to a 30% sucrose solution for at least 48 h. For verification of cannulae placement, coronal sections (60 µm) of the brains were cut using a freezing microtome, the cell bodies were stained using Cresyl Fast Violet, and the sections were viewed under a Leitz DMRD microscope and photomicrographs taken.

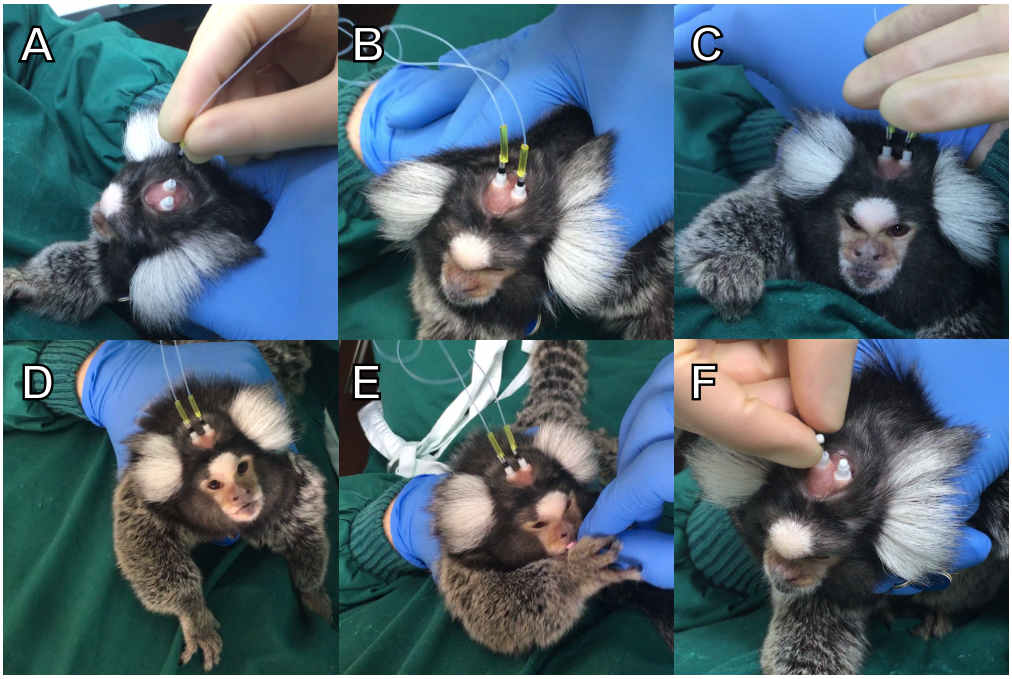

Figure 2.5.2. *Intra-cerebral infusions. Photographs of Subject 2d, one of the serial reversal animals, during a saline infusion into the caudate. A. The insertion of the injector into the guide cannula whilst a researcher holds the head still. B. Second injector has been inserted into the guide cannula. C. Injector are pushed to make sure they are flush with the guide cannula. D. Subject 2d is held loosely and allowed to move around during the procedure with no signs of distress. E. Subject 2d is fed chopped marshmallows. G. Post-infusion, dummy injectors are replaced.*

2.7 Statistical analysis

Statistical analyses were carried out using Microsoft Excel 2013, IBM SPSS Statistics Version 22 and the statistical language and environment R (R Core Team 2016).

3 Neurochemical interactions between OFC and subcortical structures and their relation to cognitive flexibility as assessed by reversal learning

3.1 Introduction

The control of behaviour is known to depend upon circuitry in both the prefrontal cortex (PFC) and in subcortical structures such as the basal ganglia and the amygdala. Broadly, the PFC is theorised to exert *top-down control* over regions of the subcortex by modulating the output of the basal ganglia and amygdala via extensive interconnections with these areas. Prefrontal top-down control has been most intensively researched in the fields of visual processing and attention, but is thought to be intrinsic to all areas of executive function and decision making, including control of the goal-directed action system (Miller and D'Esposito 2005; Gazzaley and D'Esposito 2006; Buschman and Miller 2014).

Regions of the PFC and basal ganglia, more specifically the OFC and striatum, have been identified as contributing to the process of reversal learning, and within these areas the monoaminergic neurotransmitters serotonin (5-HT) and dopamine (DA) respectively are thought to play a role. However, the contributions of the OFC 5-HT and striatal DA to reversal learning tend to be investigated separately, and thus it is unclear if there is any causal relation between the two mechanisms, namely whether OFC 5-HT exerts top-down modulation of striatal DA.

Outside the context of reversal learning, there is evidence for the PFC-mediated modulation of monoamine levels within the basal ganglia, with many early studies investigating prefrontal modulation of striatal DA (Del Arco and Mora 2009). Both pharmacological and electrical forms of PFC stimulation have been shown to enhance ventral striatal DA release (Murase et al. 1993; Karreman and Moghaddam 1996; Taber and Fibiger 1995; Taber et al. 1995; Tong et al. 1996; You et al. 1998; Del Arco et al. 2008), while intra-PFC lidocaine or intriguingly, electrical stimulation at lower, more physiologically relevant, frequencies can reduce ventral striatal DA release (Murase et al. 1993; Jackson et al. 2001). Transient increases in levels of DA and its metabolites in rat DMS have been reported following mPFC lesions (Jaskiw et al. 1990b but see Christie et al. 1986;), as well as increased DOPAC levels in the ventral striatum when rats undergo mPFC lesions in conjunction with subchronic stress (Jaskiw et al. 1990a). Excitotoxic PFC lesions were also found to attenuate amphetamine-evoked DA release in the caudate in monkeys (Wilkinson et al. 1997) and in the ventral striatum in rats (Dalley et al. 1999). Finally, there is also evidence

for PFC modulation of DA-dependent behaviours (Wolf 1998); PFC lesions can attenuate some of the sensitisation effects of cocaine and amphetamine (Wolf et al. 1995; Pierce et al. 1998; Li et al. 1999; Cador et al. 1999; Tzschentke and Schmidt 1998; 2000) while electrical stimulation of the PFC induces sensitisation (Schenk and Snow 1994), and the temporary inhibition of PFC has been demonstrated to potentiate intra-NAcc D_2-like receptor agonist-induced hyperlocomotion (Rouillon et al. 2008).

Not only do general manipulations of PFC activity alter striatal dopamine function but so too does altered dopaminergic transmission in the area. Depletion of DA in the rat mPFC has been associated with increased DA or DOPAC/DA levels in the ventral striatum (Pycock et al. 1980a; b; Carter and Pycock 1980; Martin-Iverson et al. 1986; Leccese and Lyness 1987; Thompson and Moss 1995) and dorsal striatum (Pycock et al. 1980a; b; Carter and Pycock 1980; Martin-Iverson et al. 1986), though there have also been several negative findings (Rosin et al. 1992; Hemby et al. 1992; McGregor et al. 1996; King and Finlay 1995; 1997) and it has been suggested that such changes are only seen under particular conditions such as during stress or under pharmacological stimulation (Deutch et al. 1990; King and Finlay 1997; King et al. 1997). DA depletion of PFC has also been demonstrated to induce increased DA release in the caudate in a non-human primate (Roberts et al. 1994). Intra-PFC administration of amphetamine in monkeys induced reductions in caudal levels of DA and its metabolites (Kolachana et al. 1995) and increases in DOPAC in the NAcc (Louilot et al. 1989), while a D_1 receptor antagonist increased NAcc DA levels after a delay of 24 hours (Olsen and Duvauchelle 2001). Furthermore, altered dopaminergic transmission in the PFC has been shown to modulate DA-dependent behaviours in a similar fashion to the effects of PFC lesions. Intra-PFC administration of D_2-like receptor agonists or amphetamine, but not D_1 or D_4 receptor agonists, can reduce acute amphetamine- or cocaine-induced hyperlocomotion and stereotypy (Karler et al. 1998; Prasad et al. 1999; Beyer and Steketee 2000; 2001 but see Vezina et al. 1991) and PFC DA depletion enhances hyperlocomotion (Beyer and Steketee 1999; Carter and Pycock 1980 but see Joyce et al. 1983; Clarke et al. 1988); intra-PFC administration of D_2-like receptor agonists or amphetamine also reduced behavioural sensitisation to those drugs (Ben-Shahar and Ettenberg 1998; Prasad et al. 1999; Beyer and Steketee 2002) and PFC DA depletion enhances such sensitisation (Banks and Gratton 1995). Additionally, dopaminergic transmission via D_1 receptors in the mPFC is thought to dampen NAcc D_2 receptor-mediated stress responsivity, including components of behaviour and stress-induced enhanced DA utilisation in NAcc (Doherty and Gratton 1996; Scornaiencki et al. 2009).

There are a handful of studies which specifically provided evidence for the interaction of the OFC and striatal DA. In human neuroimaging, the OFC metabolism of cocaine and methamphetamine abusers was associated with D_2 receptor availability in the striatum (Volkow et al. 1993; 2001; Volkow and Fowler 2000), while healthy subjects with the A1 allele of the *DRD2/ANKK1-Taq1A* polymorphism, which is associated with reduced striatal $D_{2/3}$ receptor binding (Thompson et al. 1997; Pohjalainen et al. 1998; Jönsson et al. 1999; Savitz et al. 2013), showed reduced glucose metabolism in the OFC, among other regions (Noble et al. 1997). Further evidence for the interaction of the OFC and striatal DA is yielded by two recent animal studies. In an investigation using their rat signal attenuation model of compulsivity, Schilman et al. 2010 found that levels of 5-HT and DA were decreased in the striatum following an excitotoxic lesion to the OFC. Finally, Clarke et al. 2014 performed DA depletions in the OFC of marmosets and demonstrated increased tonic DA levels and reduced $D_{2/3}$ receptor binding in the striatum.

Hence there is evidence in the literature that the striatal DA is modulated by the PFC, and that dopaminergic mechanisms in the PFC are involved in the modulation. The few studies that have focussed on the OFC have revealed interactions between the region and striatal DA and 5-HT. As of yet however, there have been no neurochemical investigations of the impact of 5-HT within the OFC upon monoamine levels in subcortical regions, despite the functional relevance of OFC 5-HT and striatal DA to reversal learning; for example, in a recent investigation in vervet monkeys it was found that 61% of the individual variation in reversal learning performance of the monkeys could be explained by the interaction of the levels of 5-HT in the OFC and DA in the putamen (Groman et al. 2013). In the present investigation subjects thus received unilateral 5-HT depletions of the anterior OFC using the indoleaminergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) to investigate its effects on downstream subcortical structures. After allowing sufficient time for the lesion to be fully established, the marmosets were euthanased, their brains dissected at post-mortem, and the tissue analysed for monoaminergic neurotransmitter levels via reversed-phase HPLC-ED. The small number of decussating OFC-contralateral structure projections allowed the contralateral hemisphere to be used to provide within-subject control data, i.e. subcortical regions ipsilateral to the 5-HT depletion were compared to those in the contralateral hemisphere. The nucleus accumbens, caudate and putamen were the focus of the study, with the amygdala included as an additional region of interest given the evidence that the OFC and the amygdala may interact in reversal learning (Saddoris et al. 2005; Stalnaker et al. 2007; Churchwell et al. 2009) and the extensive interconnections between the two regions (Nauta 1961; Leichnetz and Astruc 1975; Aggleton et al. 1980; Porrino et al. 1981; Amaral and Price 1984; Barbas and De Olmos 1990; Morecraft et al. 1992; Carmichael and Price 1995; Cavada et al. 2000; Stefanacci and Amaral 2000; 2002; Ghashghaei and Barbas 2002).

3.2 Methods

3.2.1 Unilateral 5,7-DHT serotonin-selective lesion of anterior OFC

Pre-surgical preparations, induction and maintenance of anaesthesia, the stereotaxic surgical procedures and the standardisation of surgical co-ordinates took place as previously described (§2.4.1, 2.4.2, 2.4.3, and 2.4.3.1 respectively). The monoaminergic neurotoxin 5,7-DHT (4μg/μl; Sigma), dissolved in saline/0.1% L-ascorbic acid, was infused into the anterior OFC (Figure 3.2.1) at the surgical co-ordinates given in Table 3.1 (adjusted for each individual marmoset using the standardisation procedure). Injections were made at either the positive or negative LM co-ordinate only to give a total of five injections. The hemisphere of the unilateral depletion was counterbalanced between monkeys, with five subjects receiving depletions of the right anterior OFC and four depletion of the left. The noradrenaline (NA) uptake blocker nisoxetine (50 mM; Sigma) and the DA uptake blocker GBR-12909 (2 mM; Sigma) were administered concomitantly in the infusate in order to protect the NA and DA innervations respectively, such that the neurotoxin selectively targeted the serotoninergic innervation.

At the completion of the surgery marmosets were sutured and allowed to recover as described previously (§2.4.4). Mild seizure activity, usually in the form of a spinal tremor, had previously been seen in the laboratory with lesions such as these, and the anti-epileptic diazepam was on hand in both oral (typical

Table 3.1. *Surgical coordinates used to create anterior OFC 5,7-DHT lesions.*

AP (in mm)	LM (in mm)	Cannula position from skull base (in mm)	Volume injected (μl)
+16.75	±2.5	0.7	0.4
	±3.5	0.7	0.4
+17.75	±2.0	0.7	0.4
	±3.0	0.7	0.4
+18.75	±2.0	0.7	0.6

AP, anteroposterior from the interaural line;
LM, mediolateral from the midline

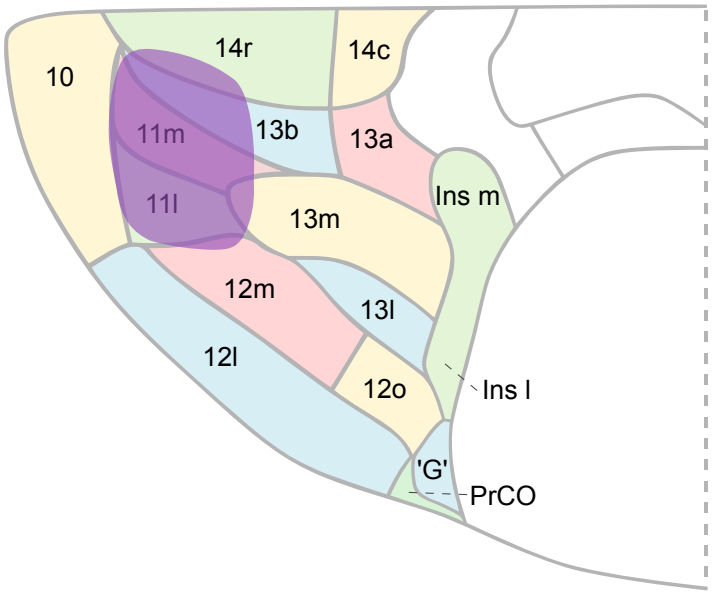

Figure 3.2.1. *Lesion of anterior OFC. Schematic of orbital surface view of marmoset brain showing cytoarchitectonic regions; purple shaded area denotes target region, centred on BA 11, for unilateral 5,7-DHT-induced depletion of 5-HT in anterior OFC.*

dose: 0.1ml of 2.5mg/5ml suspension; Rosemont Pharmaceuticals Ltd., Leeds, UK) and injectable (typical dose: 0.1ml i.m. of 10mg in 2ml solution; Hameln) forms to treat any afflicted marmosets if necessary. One of the nine subjects experienced a spinal tremor that was successfully treated with oral diazepam; diazepam caused, within minutes of being administered, seizure activity to subside and the marmosets to fall into a sleep from which they would awaken within 1-2 hours. The NACWO/NVS were consulted and heavily involved in deciding the course of treatment. Animals were to be euthanased if seizure activity became uncontrollable in order to prevent unacceptable levels of suffering, as per the terms of the project licence, and the NACWO/NVS formed a second independent and unbiased check that this state of affairs had not come about.

3.2.2 Localised brain dissection and HPLC-ED analysis

Three months post-lesion, the marmosets were euthanased (§2.6) and localised brain dissections performed according the schematics in Figures 3.2.2 and 3.2.3. The dissection and analysis had a dual aim: to determine the specificity and extent of the lesions by examining the OFC, and other nearby areas in the prefrontal cortex (PFC), for levels of the monoamines NA, DA and 5-HT, and also to investigate any potential downstream changes in subcortical areas induced by the 5,7-DHT lesion. The brain was placed placed on temperature-controlled sectioning platform (Tissue-Tek III Cryo Console; Sakura Finetek Europe B.V.; Alphen aan den Rijn, The Netherlands) held at ~3°C, and five vertical sectioning slices were used to access a range of cortical and subcortical areas. Depending on the region, the areas were removed from the slices using either a scalpel or a tissue punch. As soon as each tissue sample was isolated it was placed in a numbered Eppendorf, sealed and deposited into liquid nitrogen in an airtight vacuum flask (Plastic Dilvac Dewar Flask; Day-Impex Ltd., Colchester, UK). A key with the area, hemisphere and number of the Eppendorf was formed to keep track of the samples. The full, standardised dissection procedure is described below, though not all the regions isolated were analysed and reported.

The first of the five slices was situated 2-2.5mm posterior to the anterior pole and removed the frontal pole (Figure 3.2.2A, B and C). Five areas were then removed from the lateral surface of the frontal lobe as per Figure 3.2.2C: Brodmann area (BA) 4, BA 6, BA 8, the ventrolateral PFC which included areas 12/45 and 46, and the anterior insula. The second slice was situated 3mm posterior from the first slice, and two further regions removed; area 32 and the anterior OFC (centred on BA 11) from the medial wall and the orbitofrontal surface respectively (Figure 3.2.2A, B). The third slice was situated another 3 mm posterior from the second slice and anterior regions of the basal ganglia which included the ventromedial caudate (vm caudate), dorsolateral caudate (dl caudate), the anterior putamen and the NAcc, and cortical regions which included the anterior cingulate, posterior OFC, mid-insula and area 25, were removed. The fourth slice was a further 3mm from the third slice and the mid-cingulate, posterior caudate, posterior putamen, amygdala, BNST and hypothalamus regions were removed (Figure 3.2.3). The fifth and final slice was taken another 3mm from the fourth slice, and the temporal lobe unravelled to reveal the hippocampus.

Tissue samples were transferred from the liquid nitrogen to a tray of dry ice. From here the samples were moved into polythene bags labelled by area and stored at -80°C before being analysed using reversed-phase HPLC-ED, the protocol for which has been described previously (Clarke et al. 2004; 2005; 2007; Man et al. 2010; Mikheenko et al. 2015). The sorting and labelling of samples was pivotal for two reasons. Firstly, that despite environmental conditions being kept as constant as was possible, the HPLC system fluctuated slightly across the day according to variation in factors such as temperature. As the monoamine levels in each area were being directly contrasted with the levels in the corresponding region in the contralateral hemisphere, running the analysis of monoamine levels in the same region in both hemispheres consecutively minimised noise that would otherwise have made comparison more difficult. Secondly, the HPLC system had to be calibrated using standards of known concentrations of NA, DA and 5-HT. These formed the easiest and most accurate comparison when they were of a similar concentration to those found in the tissue itself. Since levels of DA and 5-HT in particular could vary by an order of magnitude between the cortical and subcortical regions (low DA and high 5-HT in the cortex, high DA and low 5-HT

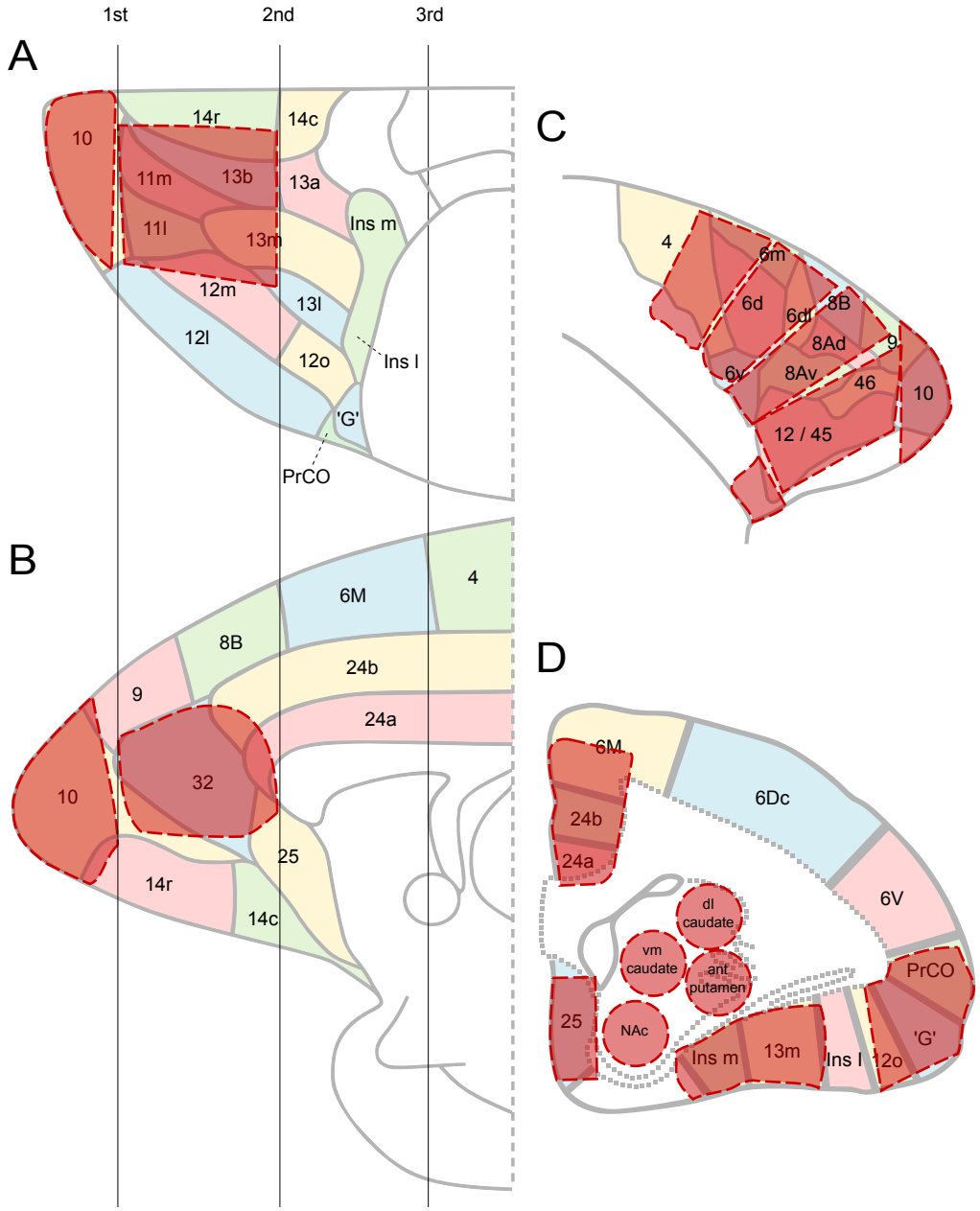

Figure 3.2.2. *Localised dissection of anterior portion of brain. Schematic diagrams show cytoarchitectonic regions of the marmoset brain from differing views, with regions removed shaded in red. A, B. Orbital surface and medial views of marmoset brain showing the positions of the first three vertical sectioning slices. A. Orbital surface view. Regions removed frontal pole (left) and anterior OFC (right). B. Medial view. Regions removed are frontal pole (left) and area 32 (right). C. Side view of frontal lobe showing the removal of the frontal pole in the first vertical sectioning slice (far right). Other regions shown are removed from the cortical surface; they are, clockwise from top left: BA 4, BA 6, BA 8, ventrolateral PFC and the anterior insula. D. Coronal section taken at the level of the third vertical sectioning slice showing anterior subcortical regions taken and four cortical areas. Cortical areas removed are, clockwise from top left: anterior cingulate, posterior OFC, mid-insula and area 25. Outlines of regions drawn according to diagrams by Prof. Angela C. Roberts.*

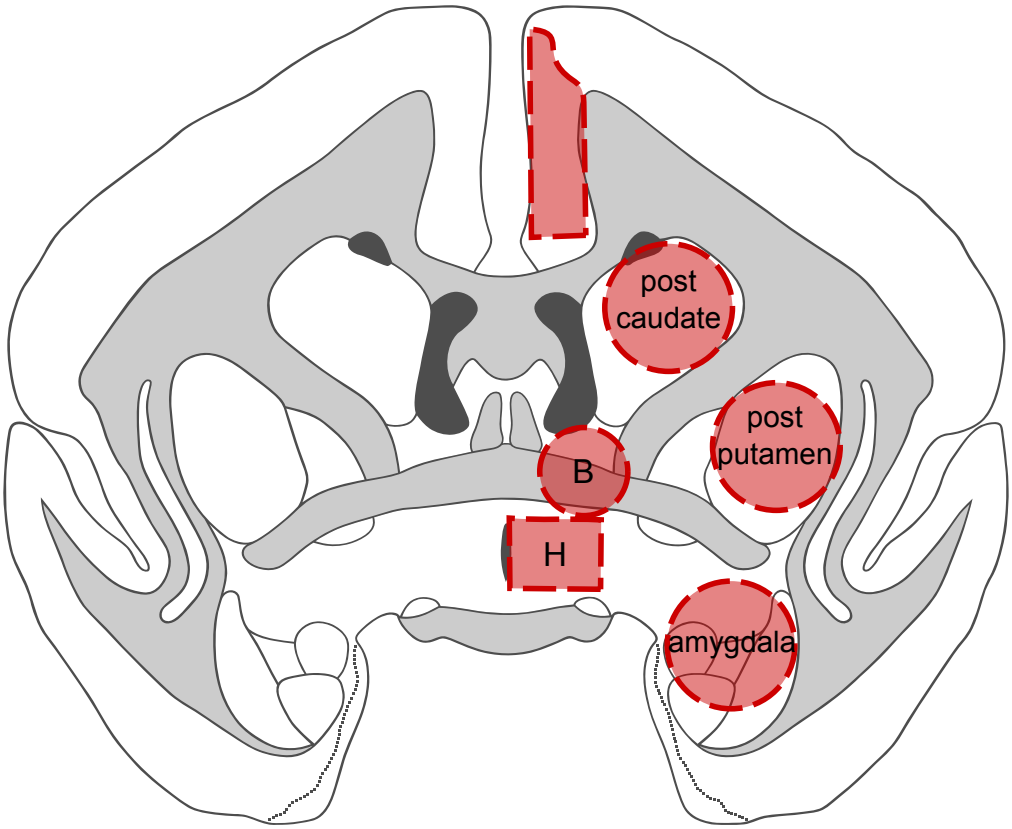

Figure 3.2.3. *Localised dissection of posterior portion of brain. Coronal section at the level of the fourth vertical sectioning slice, 3mm posterior from the third vertical sectioning slice. Sections taken are, clockwise from top left: mid cingulate (unlabelled), posterior caudate, posterior putamen, amygdala, BNST (B), and the hypothalamus (H).*

in the subcortex), regions were grouped together into cortical and subcortical categories to facilitate the use of appropriate standards.

Tissue samples were defrosted, homogenised in 200µl of 0.2 M perchloric acid, and centrifuged at 6000 rpm for 20 min at 4°C to produce a supernatant suitable for HPLC analysis. Chilled 15µl samples were separated on a C18 silica-based analytical column (100 x 4.6mm 3µm octadecylsilane) using a mobile phase (13.6g/l $KH_2PO_4.H_20$, 185 mg/l octane sulfonic acid, and 18% methanol, pH 2.75) delivered at 0.8ml/min. Tissue levels of DA and 5-HT, their respective metabolites DOPAC and 5-hydroxyindoleacetic acid, and NA, were quantified using a dual-electrode analytical cell and electrochemical detector (Coulochem II; ESA, Chelmsford, MA) with electrode 1 set at 150 mV and electrode 2 set at 180 mV (5014b analytical cell; ESA) with reference to a palladium electrode. The resultant signal was integrated using Chromeleon software (version 6.20; Dionex, Sunnyvale, California, USA).

3.3 Results

3.3.1 Serotoninergic depletion was neurochemically specific and mostly localised to the OFC

Four animals were excluded from analysis: two subjects had lesions the location of which was too anterior and did not cover the whole of the target region, and in two subjects the lesion failed to produce a sufficient depletion. In the remaining five subjects 5-HT depletion of the anterior OFC was consistent and robust; depletions of 60-76% of 5-HT were seen in the anterior OFC of the depleted hemisphere relative to the non-depleted hemisphere. There was some spread of the lesion into nearby areas, namely the vlPFC and the pgACC, though depletions in these areas were of a smaller magnitude than those seen in the anterior OFC, and were more variable between subjects (Figure 3.3.1, Table 3.3).

Table 3.2. *Percentage depletions of serotonin across the anterior OFC and nearby areas, depleted hemisphere relative to non-depleted hemisphere. Means and standard deviations given.*

Region	Percentage depletion
Anterior OFC	65.1 ± 6.38
vlPFC	42.4 ± 9.43
pgACC	33.7 ± 19.5
Frontal pole	8.53 ± 142
Anterior insula	9.37 ± 10.0
Posterior OFC	-46.6 ± 54.0

In order to analyse the specificity of the lesion, 5-HT depletion was first assessed in the anterior OFC, for which there was an obvious *a priori* interest. Given the pattern of spread of the lesion into nearby ventral regions of the PFC that been seen previously in my laboratory with this type of lesion (Clarke et al. 2007) there was also an *a priori* interest in a number of regions surrounding the anterior OFC, and so the level of 5-HT depletion was checked in the vlPFC, pgACC, frontal pole, anterior insula and posterior OFC. 5-HT depletion in each area was assessed using individual one-sample t-tests which compared the ratio of the 5-HT level in the depleted and non-depleted hemispheres, i.e. $\frac{5HT\ in\ depleted\ hemisphere}{5HT\ in\ nondepleted\ hemisphere}$, against a value of 1 (indicative of no difference between the levels in each hemisphere). 5-HT levels were found to be significantly depleted in the anterior OFC (t_4 = -22.8; p=0.0000219), as well as the vlPFC (t_4

Table 3.3. *Raw data showing serotonin levels in anterior OFC and nearby frontal regions following unilateral anterior OFC 5-HT depletion. Levels shown in the lesioned and control hemispheres per subject in units of pmoles/mg tissue to 3 significant figures.*

	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
Region	C	L	C	L	C	L	C	L	C	L
Anterior OFC	0.781	0.193	1.35	0.529	0.845	0.329	0.568	0.224	0.655	0.213
vlPFC	0.512	0.313	0.951	0.676	0.597	0.428	0.280	0.172	0.497	0.423
pgACC	0.693	0.277	0.780	0.550	1.04	0.703	*	0.363	0.801	0.695
Frontal pole	0.951	0.197	1.17	0.258	2.33	0.515	0.518	0.248	0.247	0.850
Anterior insula	0.819	0.767	1.32	1.10	1.42	1.51	0.672	0.592	0.782	0.636
Posterior OFC	*	*	1.20	1.18	1.15	1.93	0.837	1.79	0.842	0.901

* denotes data points lost during tissue processing

= -10.0; p=0.000553) and pgACC (t_3 = -3.46; p=0.0405), while changes in the frontal pole (t_4 = -0.134; p=0.890), anterior insula (t_4 = -2.09; p=0.105) and posterior OFC (t_3 = 1.73; p=0.183) were not found to be significant. Cohen's d was calculated to give effect sizes for the significant depletions in the anterior OFC, vlPFC and pgACC with results of d=-10.2, -4.49 and -1.73 respectively, confirming that the magnitude of the 5-HT depletion was greatest in the anterior OFC.

Table 3.4. *Percentage depletions of serotonin, dopamine and noradrenaline levels in the anterior OFC, depleted hemisphere relative to non-depleted hemisphere. Means and standard deviations given.*

Neurotransmitter	Percentage depletion
Serotonin	65.1 ± 6.38
Dopamine	6.08 ± 17.7
Noradrenaline	15.9 ± 13.9

5-HT depletion within the anterior OFC was found to be neurochemically specific with no consistent depletions seen in levels of DA or NA (Figure 3.3.2 and Table 3.4). A mixed model ANOVA with percentage depletion of 5-HT as the dependent variable, and neurotransmitter and subjects as fixed and random factors respectively showed a main effect of neurotransmitter ($F_{2,8.00}$ = 31.8; p=0.000156). One-sample t-tests comparing percentage depletion of each neurotransmitter across subjects to a value of 0% revealed that only the the 5-HT depletion was significant (t_4 = -22.8; p=0.0000219) and not the changes in DA (t_4 = 0.767; p=0.486) or NA (t_4 = 2.56; p=0.0626).

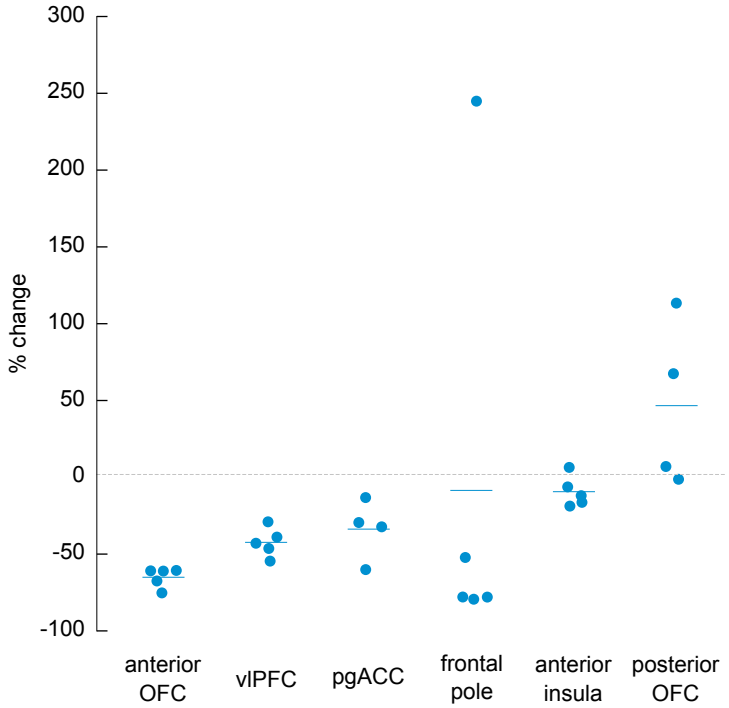

Figure 3.3.1. *Percentage change in 5-HT levels in depleted hemisphere relative to nondepleted hemisphere, across the OFC and nearby areas. Horizontal bars denote mean and circles represent individual data points from each of the five subjects.*

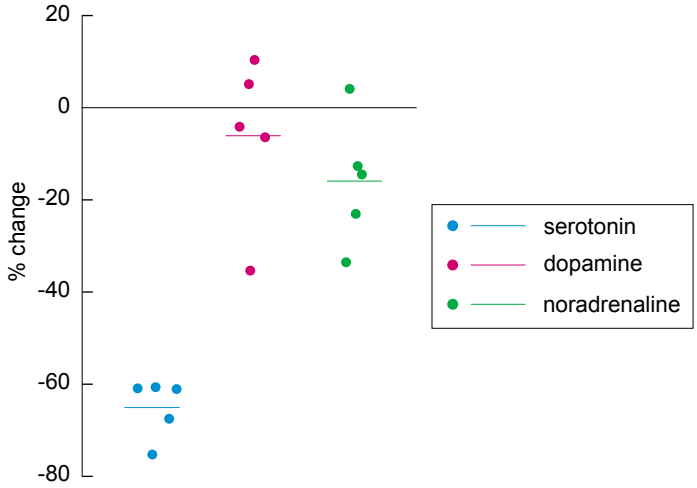

Figure 3.3.2. *Percentage change in levels of serotonin, dopamine and noradrenaline in the depleted hemisphere relative to the nondepleted hemisphere within the anterior OFC. Horizontal bars denote mean and circles represent individual data points from each of the five subjects.*

3.3.2 OFC serotonin depletion caused dopamine upregulation in the amygdala but not striatum

Table 3.5. *Percentage change in levels of serotonin and dopamine, in the depleted hemisphere relative to nondepleted hemisphere, in subcortical regions including the striatum and amygdala. Means and standard deviations given.*

	Percentage change	
Region	Serotonin	Dopamine
Dorsolateral caudate	12.3 ± 14.2	5.62 ± 18.8
Ventromedial caudate	16.3 ± 14.2	1.71 ± 2.81
Caudate body	55.0 ± 39.9	39.6 ± 23.3
Central putamen	20.8 ± 12.9	22.0 ± 18.2
Posterior putamen	-4.90 ± 5.89	2.23 ± 16.4
Nucleus accumbens	-1.62 ± 17.8	32.8 ± 49.5
Amygdala	35.4 ± 27.5	172 ± 45.8

A range of subcortical regions, including dorsolateral and ventromedial portions of the head of the caudate, the caudate body, the central and posterior putamen, the nucleus accumbens and the amygdala, were examined for changes in 5-HT or DA following unilateral 5-HT depletion. Noradrenaline was only present in these regions at very low levels that were below the threshold for detection with the HPLC-ED analysis, and so noradrenergic changes were not examined. No consistent serotoninergic or dopaminergic changes were seen in any of the striatal regions, while dopamine, but not serotonin, levels were significantly increased in the amygdala (Figure 3.3.3; Tables 3.5, 3.6 and 3.7). Individual one-sample t-tests were run to compare the ratios of 5-HT and DA in the depleted and non-depleted areas against a value of 1 (see §3.3.1), which confirmed that the amygdala dopaminergic increase was significant ($t_4 = 3.76$; p=0.0198) and that there were no other significant changes in the striatal areas (Table 3.8).

3.4 Discussion

The unilateral depletion of 5-HT within the anterior OFC in a cohort of common marmosets was achieved successfully, with no consistent changes in DA or NA levels seen within the anterior OFC and only minimal spread of the lesion into the nearby regions of the vlPFC and pgACC. Subsequent brain dissection and HPLC-ED analysis of subcortical regions, with levels in areas ipsilateral to the OFC 5-HT depletion compared against corresponding areas in contralateral non-depleted hemisphere, revealed that OFC serotoninergic depletion induced dopaminergic upregulation in the amygdala, but did not affect DA nor 5-HT levels in the striatum.

The use of unilateral 5,7-DHT lesions allowed the comparison of subcortical regions in the depleted hemisphere relative to the non-depleted hemisphere, thus permitting each subject to be used as their own control. Variation resulting from individual differences in monoamine levels was thus hugely lessened, and if the feature had not been implemented the number of animals that it would have been necessary to include in order to see effects against a backdrop of between-subject variation would have likely made the experiment infeasible. Spread of the lesion into nearby ventral regions of the PFC had been seen previously in my laboratory with this type of lesion (Clarke et al. 2004; 2005; 2007), and was the case in this experiment, with percentage depletions of 42.4 ± 9.43 seen in the vlPFC and 33.7 ± 19.5 in the pgACC, compared to a percentage depletion of 65.1 ± 6.38 in the target region of the anterior OFC. Though the strongest

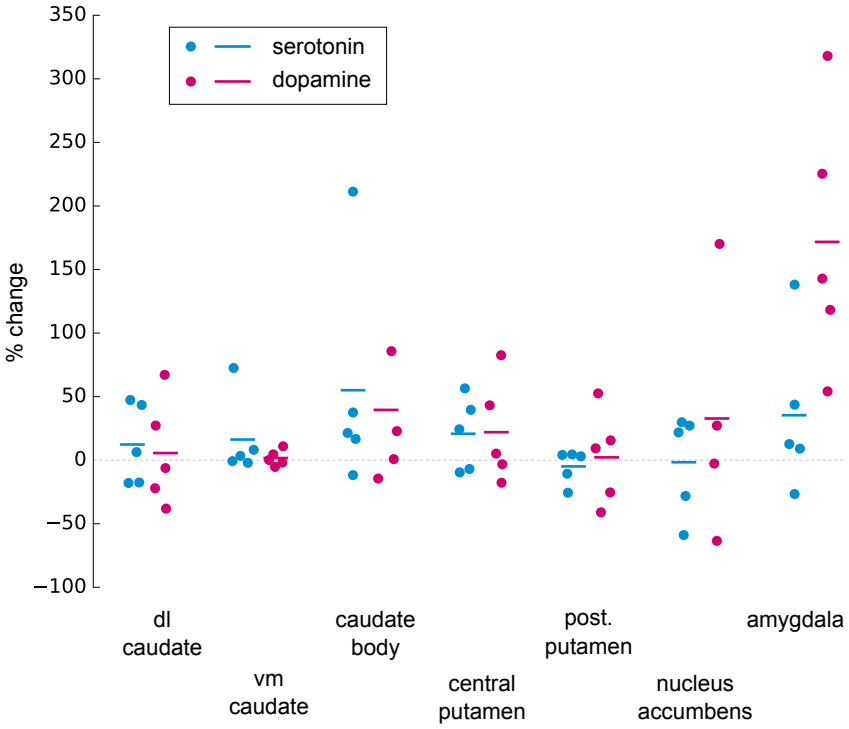

Figure 3.3.3. *Percentage change in levels of serotonin and dopamine, in the depleted hemisphere relative to nondepleted hemisphere, in subcortical regions including the striatum and amygdala. Horizontal bars denote mean and circles represent individual data points from each of the five subjects.*

and most consistent depletion was found in the target region, it is impossible to definitely state that this depletion, and this depletion alone, was responsible for the observed downregulation of amygdala DA.

There is a wealth of evidence in the literature that regions within the PFC act to modulate levels of DA within the striatum. Some studies have identified the OFC to be one such prefrontal region (Schilman et al. 2010), and within the OFC levels of DA have been further specified to be involved in the modulation (Clarke et al. 2014). Comparison of this previous work with the negative results with respect to the striatum seen in the present investigation allows the inference that the OFC dopaminergic modulation of striatal DA is neurochemically specific; 5-HT depletion within the OFC appears to have no downstream effect upon levels of DA within any part of the striatum, in stark contrast to the effect of DA depletion. It can thus be reasoned that it is unlikely that reversal learning deficits following OFC 5-HT depletion (Clarke et al. 2004; 2005; 2007) are effected via altered downstream monoaminergic activity in the striatum, and instead that OFC 5-HT and striatal DA contribute to reversal learning performance independently. Such a conclusion appears at odds with data from Groman et al. 2013, in which it was found that the interaction of OFC 5-HT and putamen DA levels, but not OFC 5-HT nor putamen DA levels alone, accounted for a substantial proportion of the variance in reversal learning performance. Further research is needed to resolve the apparently conflicting datasets.

In contrast to the negative striatal results, substantial increases were demonstrated in amygdala DA levels. The OFC and amygdala have long been known to be highly interconnected (Ghashghaei and Barbas 2002; Barbas 2007), and have been associated at a functional level, particularly in studies of emotion and anxiety

(Banks et al. 2007; Liang et al. 2009; Versace et al. 2010; Hahn et al. 2011; Sladky et al. 2015; Gold et al. 2015), but there has been relatively little focus on the neurochemical interactions between the two regions. That amygdala DA levels increase following OFC 5-HT depletion is thus a novel finding which provides new insight into the nature of the modulation of the amygdala by the OFC. With regard to reversal learning, the result raises the possibility that reversal learning deficits following OFC 5-HT depletion are mediated through changes in amygdala DA, a prospect that receives partial support from previous reports that the amygdala, in conjunction with the OFC, does play a role in reversal learning (Saddoris et al. 2005; Stalnaker et al. 2007; Churchwell et al. 2009; Chau et al. 2015). That the OFC and the amygdala interact is agreed upon by the multiple groups working to investigate their joint involvement in reversal learning, but there are several different theories of the nature of the relationship between the two regions: Schoenbaum and colleagues advocate that the OFC encodes prior action-outcome associations which drive the flexible encoding of new associations in the amygdala via error signals (Schoenbaum et al. 2009), Morrison and Salzman and colleagues that the relative contribution of the OFC and the amygdala is valence dependent (Morrison et al. 2011), and Rushworth and colleagues that the interaction of the regions acts to emphasise relevant rewards relative to irrelevant rewards in the process of credit assignment (Chau et al. 2015). The findings in this chapter could be argued to suggest a fourth possibility, based upon the prior work of Clarke et al. 2007, that OFC serotonin, via the upregulation of amygdala DA, is involved in the inhibition of prepotent responses to previously rewarded stimuli.

The findings in the present study complement the work that has been done elsewhere in the literature to attempt to characterise the interaction of the OFC and amygdala. There have been numerous efforts to establish how the two regions relate to one another electrophysiologically (Saddoris et al. 2005; Schoenbaum and Roesch 2005; Stalnaker et al. 2007; Schoenbaum et al. 2009), but to my knowledge this is the first attempt to uncover the neurochemical relationship between the regions.

Table 3.6. *Raw data showing serotonin levels in the subcortical regions following unilateral anterior OFC 5-HT depletion. Levels shown in the lesioned and control hemispheres per subject in units of pmoles/mg tissue to 3 significant figures.*

	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
Region	C	L	C	L	C	L	C	L	C	L
Dorsolateral caudate	1.09	0.891	0.545	0.782	1.27	1.35	0.565	0.467	0.410	0.605
Ventromedial caudate	1.45	1.42	1.22	1.26	1.57	1.70	0.716	0.710	0.721	1.24
Caudate body	1.17	1.60	1.37	1.21	1.53	4.77	0.663	0.805	0.734	0.856
Central putamen	1.10	1.53	1.19	1.86	2.60	3.23	1.49	1.39	1.16	1.05
Posterior putamen	1.47	1.53	2.08	2.17	2.26	1.68	1.21	1.25	1.21	1.08
Nucleus accumbens	3.22	2.31	1.54	1.96	3.36	1.38	0.815	1.06	1.33	1.62
Amygdala	1.87	4.44	4.58	6.58	2.45	2.68	1.60	1.18	1.68	1.90

Table 3.7. *Raw data showing dopamine levels in the subcortical regions following unilateral anterior OFC dopamine depletion. Levels shown in the lesioned and control hemispheres per subject in units of pmoles/mg tissue to 3 significant figures.*

	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
Region	C	L	C	L	C	L	C	L	C	L
Dorsolateral caudate	53.2	33.0	19.5	24.9	38.4	36.0	26.8	20.9	15.5	25.9
Ventromedial caudate	54.5	60.4	48.5	45.9	41.8	43.7	38.5	37.8	37.4	37.4
Caudate body	54.7	46.8	56.4	56.8	64.4	131	19.8	36.8	18.9	23.82
Central putamen	31.3	57.1	32.9	47.1	47.5	45.9	43.7	36.0	31.3	33.0
Posterior putamen	41.9	45.8	44.2	51.1	48.6	36.3	50.4	29.7	29.0	44.2
Nucleus accumbens	11.8	32.0	45.8	58.3	33.7	32.9	32.9*	1.86*	43.5	15.9
Amygdala	1.28	5.36	3.22	7.80	1.41	3.08	0.879	2.86	1.28	1.98

* denotes anomalous values excluded from analysis

Table 3.8. *Results from one-sample t-tests comparing the ratio of the level of 5-HT/DA in the depleted hemisphere and that in the nondepleted hemisphere with a value of 1 in subcortical regions following unilateral anterior OFC 5-HT depletion.*

Region	Neurotransmitter	t-test result
Amygdala	Dopamine	$t_4 = 3.76$; p=0.0198
	Serotonin	$t_4 = 1.26$; p=0.275
Dorsolateral caudate	Dopamine	$t_4 = 0.299$; p=0.78
	Serotonin	$t_4 = 0.868$; p=0.434
Ventromedial caudate	Dopamine	$t_4 = 0.610$; p=0.575
	Serotonin	$t_4 = 1.15$; p=0.316
Caudate body	Dopamine	$t_4 = 1.70$; p=0.164
	Serotonin	$t_4 = 1.38$; p=0.239
Central putamen	Dopamine	$t_4 = 1.21$; p=0.293
	Serotonin	$t_4 = 1.61$; p=0.182
Posterior putamen	Dopamine	$t_4 = 0.136$; p=0.898
	Serotonin	$t_4 = -0.831$; p=0.453
Nucleus accumbens	Dopamine	$t_4 = 1.09$; p=0.336
	Serotonin	$t_4 = -0.0907$; p=0.932

4 Parsing the differential contribution of primate striatal regions to serial reversal learning

4.1 Introduction

Reversal learning is a simple task in widespread use as an assay of cognitive flexibility (Izquierdo et al. 2016a). A paradigm with great translational potential, reversal learning can be implemented across a variety of species, including most commonly mice (Bissonette and Powell 2012), rats (Pubols 1956; Brookshire et al. 1961; Stevens 1973), monkeys (Zola and Mahut 1973; Higuchi 1982; Rumbaugh and McQueeney 1963; Cross and Brown 1965; Jentsch et al. 2002; Ridley et al. 1985) and humans (Vaughter and Cross 1965), but also species as diverse as worms (Datta 1962), cockroaches (Longo 1964), woodlice (Thompson 1957; Harless 1967), bees (Chittka 1998; Komischke et al. 2002; Mota and Giurfa 2010; Strang and Sherry 2014), spiders (Liedtke and Schneider 2014), lizards (Day et al. 1999), turtles (Kirk and Bitterman 1962; Holmes and Bitterman 1966; Ishida and Doi 1996), crabs (Datta et al. 1960), fish (Bitterman et al. 1958; Warren 1960; Behrend et al. 1965; Setterington and Bishop 1967; Mackintosh and Cauty 1971; Lucon-Xiccato and Bisazza 2014), many types of bird including pigeons, chickens and crows (Reid 1958; Warren et al. 1960; Bullock and Bitterman 1962; Gossette et al. 1966a; Gossette et al. 1966b; Stettner et al. 1966; Beale 1970), bats (Ellins and Masterson 1971), squirrels (Chow et al. 2015), ferrets (Hughes 1964), raccoons (Warren and Warren 1962), cats (Cronholm et al. 1960; Beck et al. 1966), dogs (Tapp et al. 2003), horses (Warren and Warren 1962; Fiske and Potter 1979), and octopuses (Young 1962a; b; Mackintosh and Mackintosh 1963). Findings of altered cognitive flexibility across a range of neuropsychiatric disorders have fueled such translational investigation into the neural and psychological underpinnings of the task, and consequently, our current understanding is borne from an extensive body of work spanning decades of research.

Despite such intensive research, our knowledge of the neural basis of reversal learning is far from complete. Whilst the OFC is widely accepted to be critical to reversal learning (Clarke et al. 2004; Rudebeck and Murray 2014; Hamilton and Brigman 2015), the contribution of the striatum, a region which receives strong projections from the OFC (Roberts et al. 2007; Schilman et al. 2008), to execution of the task is still unclear. The striatum is commonly subdivided into dorsal and ventral portions, the later of which includes the nucleus accumbens (NAcc). The dorsal striatum is further subdivided in most mammals into two regions, the more medial caudate nucleus and the more lateral putamen, which are separated by the white matter tracts of the internal capsule (Albin et al. 1989; DeLong 2000). In rodents however, the dorsal striatum exists anatomically as an single structure undivided by any white matter, though the

medial and lateral portions, known as the dorsomedial striatum (DMS) and dorsolateral striatum (DLS), have been found in many studies to differ in terms of function (e.g. Moussa et al. 2011; Ito and Doya 2015) and are widely considered to be homologous to the caudate and the putamen respectively of the primate (Balleine and O'Doherty 2010). There is confusion in the literature as to the precise anatomical subregion of the striatum involved in reversal learning. For example, different human neuroimaging studies have identified both dorsal (caudate; Rogers et al. 2000; Ghahremani et al. 2010) and ventral striatal (Cools et al. 2002) recruitment during reversal learning.

Multiple animal studies support a role for the dorsal striatum in reversal learning. Lesions situated at different locations within the region induce reversal learning deficits across several species, including the caudate nucleus in rhesus monkeys (Divac et al. 1967), the medial striatum (comprising the medial head of the caudate nucleus in conjunction with the NAcc) in marmosets (Clarke et al. 2008), and the dorsal striatum of the rat (entire area: Kolb 1977 but see Ferry et al. 2000; restricted to DMS Kirkby 1969; Pisa and Cyr 1990; Castañé et al. 2010), as does the inactivation of the rat DMS (Ragozzino et al. 2002; Ragozzino and Choi 2004; Ragozzino 2007). Furthermore, extracellular acetylcholine levels have been shown to transiently increase in the DMS as rats learn to respond to the previously unrewarded stimulus (Ragozzino and Choi 2004; Palencia and Ragozzino 2006; Ragozzino et al. 2009), and the intra-DMS administration of muscarinic cholinergic receptor agonists or antagonists impairs reversal learning (Ragozzino et al. 2002; 2009), with the former being shown to be blocked by the concomitant infusion of an antagonist (Ragozzino et al. 2009). The intra-DMS infusion of an NMDA antagonist also impaired reversal learning (Palencia and Ragozzino 2004; Palencia and Ragozzino 2006), as well as blocking the transient increase in acetylcholine efflux (Palencia and Ragozzino 2006). In a PET study of reversal learning conducted with vervet monkeys, greater D_2-like dopamine receptor availability in both the caudate and putamen, but not the ventral striatum, was found to associate with better reversal learning performance (Groman et al. 2011).

There is also evidence which points to a role for the nucleus accumbens (NAcc) in reversal learning. Early studies in rats and monkeys showed that excitotoxic lesions or depletion of DA in the NAcc gave reversal learning deficits (Taghzouti et al. 1985; Annett et al. 1989; Stern and Passingham 1995; Ferry et al. 2000 but see Burk and Mair 2001; Schoenbaum and Setlow 2003; Castañé et al. 2010), as does the intra-NAcc administration of a $D_{2/3}$receptor agonist (Haluk and Floresco 2009). Work characterising neuropsychological dysfunction in Parkinson's Disease (PD) also supports such a localisation of function. In PD, the progressive degeneration of dopaminergic neurons within the substantia nigra (SN) causes DA depletion downstream in the striatum, resulting in a characteristic array of motor deficits which include tremor, bradykinesia, rigidity and postural instability, in addition to deficits in cognition (Dauer and Przedborski 2003; Jankovic 2008; Kalia and Lang 2015). In contrast to those within the SN, dopaminergic neurons in the ventral tegmental area (VTA) are relatively spared, particularly early on in the disease, and thus the primarily SN-innervated dorsal striatum is much more severely depleted of DA than the VTA-innervated ventral striatum (Kish et al. 1988). In the "dopamine overdose" hypothesis (Gotham et al. 1986; 1988; Cools et al. 2001b) it is theorised that such spatio-temporal patterns of progression of DA depletion can explain the profile of cognitive deficits seen in early PD, both on and off dopaminergic mediation (Owen 2004; Cools 2006; 2007; Macdonald and Monchi 2011). Unmedicated PD patients show impairments

in neuropsychological tasks such as task switching (Hayes et al. 1998; Cools et al. 2001a), thought to be dependent upon the dorsal striatum, deficits which can then be ameliorated by the administration of the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA) (Cools et al. 2001b; 2003; Shook et al. 2005). Conversely, the receipt of L-DOPA worsens reversal learning in PD patients (Swainson et al. 2000; Cools et al. 2001b; 2006; Graef et al. 2010; Macdonald et al. 2013; Buelow et al. 2015), and this effect has been replicated in healthy volunteers (Vo et al. 2016). It is thought that while the L-DOPA-induced augmentation of DA levels in the dorsal striatum is beneficial and normalises function, the DA-replete ventral striatum becomes "overdosed" as DA levels are raised to a counterproductive height (Owen 2004; Cools 2006; 2007; MacDonald et al. 2011). Direct evidence for the hypothesis was supplied in a neuroimaging study in which L-DOPA was found to modulate reversal-related activity in the NAcc of PD patients (Cools et al. 2007).

The aim of the present investigation was thus to clarify the contribution of subregions of the striatum to reversal learning, focussing on the dorsal but not ventral striatum in light of the more equivocal and/or indirect nature of the evidence for the contribution of the latter. In a previous marmoset study from my laboratory, the ventromedial caudate (vm caudate) was found to contribute to reversal learning, with dopaminergic depletion of the region inducing a reversal learning deficit (Clarke et al. 2011). In contrast, recently published findings concerning the vervet monkey showed that 61% of the individual variation in reversal learning performance of the animals could be explained by the interaction of the levels of 5-HT in the OFC and DA in the putamen (Groman et al. 2013). The results of the Groman et al. 2013 study tallied closely with data from my laboratory in which OFC serotonin (Clarke et al. 2004; 2005; 2007) and striatal dopamine (Clarke et al. 2011), as above, had been linked to reversal learning, but with the distinction that it was the putamen and not the caudate that appeared to be the critical locus.

In order to follow-up these results marmosets were trained on a serial reversal learning paradigm (Rygula et al. 2010), the structure of which supported the use of repeated, acute manipulations. Marmosets were given a discrimination in which responding to one of the two stimuli was paired with reward and responding to the other a mild punishment, response-outcome contingencies which were reversed daily. Over time, subjects developed a stable baseline level of responding against which performance following acute interventions could be compared. The task also comprised a daily retention phase which preceded the reversal phase in which the response-outcome contingencies were identical to those of the reversal phase of the previous day, a feature which made it possible to isolate impairments specific to reversal learning from any more general deficits which would affect performance in both phases of the task. Marmosets were implanted with indwelling cerebral cannulae targeting the ventromedial caudate and putamen, and the regions were then reversibly inactivated using the $GABA_A$ agonist muscimol.

4.2 Methods

4.2.1 Serial reversal learning task

Four marmosets took part in the study: Subjects 2a-d, all male. Marmosets were given preliminary behavioural training on the touchscreen (§2.3; "Pre-training" in Figure 4.2.1) before being trained and tested

Table 4.1. *Number of sessions spent across training phases per subject in the serial reversal paradigm*

Subject	Number of sessions		
	Preliminary touch training	Training discrimination	"Between-session reversals"
Subject 2a	151	14	32
Subject 2b	25	6	24
Subject 2c	20	1	13
Subject 2d	50	4	23

on the serial reversal learning paradigm (Figure 4.2.1), which has previously been described (Rygula et al. 2010).

During serial reversal training and testing, subjects had daily testing sessions between Monday to Friday. A trial consisted of two stimuli being presented on the touchscreen, on the left and right hand sides, until one was touched by the marmoset. If the marmoset touched the correct stimulus, an auditory cue of a recording of birdsong would play, signalling availability of banana milkshake reward for five seconds, and the incorrect stimulus would disappear from the screen whilst the correct stimulus remained present. If the marmoset touched the incorrect stimulus both stimuli disappeared from the screen, the houselight was turned off for a five second timeout "punishment darkness", and a mildly aversive auditory cue was played. The brief, mildly aversive loud noise was 0.3s long at a volume of ~100dB. The ITI remained the same as in the final stages of preliminary behavioural training, i.e. 3 seconds in duration.

After completing the preliminary behavioural training on the touchscreen, subjects were given a pair of training stimuli with which they learnt to discriminate (Table 4.1). Once they could successfully discriminate between the training stimuli they moved to the main discriminative set (Figure 4.2.1B), and were trained to reverse the discrimination (Table 4.1). Each session terminated after a subject reached the criterion of six consecutive correct responses to pass the session, or failing that, after 20 minutes. When the marmoset passed the session, in the session of the following day the stimulus-reward contingencies were reversed such that the previously correct stimulus became incorrect and the previously incorrect stimulus became correct. Marmosets were tested on the new stimulus-reward contingencies until they passed the session again. The response-outcome contingencies were again reversed for the subsequent session, and marmosets continued to be tested on these "between-session reversals" until they could consistently, upon receiving new response-outcome contingencies, pass the session that day, a "same-day pass". Marmosets were then moved to "within-session reversals" when they had achieved 10 same-day passes in between-session reversals, though these did not need to be consecutive.

Within-session reversals comprised a retention phase where response-outcome contingencies were the same as those of the previous day, and a reversal phase, where they were inverted. When marmosets reached a behavioural criterion of six correct responses within seven trials the retention phase was passed, the response-outcome contingencies changed and the reversal phase began (Figure 4.2.1B). There were no environmental signals that cued the transition between phases other than the change in response-outcome contingencies. The testing session terminated when marmosets reached the criterion of six consecutive

correct responses, or failing that after 20 minutes. In the event that a subject did not pass the retention phase of a session, the response-outcome contingencies at the beginning of the retention phase of the next session would remain the same as those of the previous day's failed retention phase. In the event that a subject did not pass the reversal phase of the session, the response-outcome contingencies of the following day's retention phase began were the same as those in the failed reversal phase (thus failing the reversal phase had no effect upon the next day's response-outcome contingencies). Once a marmoset had exhibited stable reversal performance, as defined by the successful completion of ten within-session reversals, they underwent cannulation surgery (§4.2.2), and after recovery, received intra-striatal infusions of the $GABA_A$ agonist muscimol to inactivate the putamen or caudate on probe serial reversal sessions (§4.2.3).

The main behavioural measure used to assess the role of the striatal areas in reversal learning was the number and distribution of errors in the reversal phase of the task, which were plotted against trials to form learning curve graphs (§4.3). A key attribute of the paradigm was that effects on the specific psychological process of reversing the response-outcome contingencies could be identified; if inactivating an area led to normal performance in the retention phase of a session but a deficit in the reversal phase, the dysfunction must be to do with reversal and not caused by more general deficits in the subordinate processes of attention, discrimination or motivation, deficits which would adversely affect performance in both the retention and reversal phases.

4.2.2 Striatal cannulation

The marmosets were implanted with indwelling cannulae which targeted the ventromedial caudate and the putamen; the double guide cannulae were adapted so that one guide was longer than the other, with the 8mm and 9mm guides targeting the ventromedial caudate and putamen respectively at co-ordinates of AP + 11, LM ± 2.55, V + 10.5 and AP + 11, LM ± 4.95, V + 9.5 (Figure 4.2.2). Again, surgical procedures including preparations, induction and maintenance of anaesthesia, stereotaxic surgical technique and post-operative care were the same as previously described (§2.4.1, 2.4.2, 2.4.3, and 2.4.4 respectively).

4.2.3 Intra-striatal muscimol infusions

Marmosets received intra-striatal infusions of muscimol, at doses ranging from 0.03 - 0.3µg muscimol in 0.5µl saline (Aquapharm sodium chloride 0.9% w.v.; Animalcare Ltd.) according to the infusion procedures already described (§2.5.1).

The spread of muscimol in this experiment was not measured directly. Direct measurement of muscimol spread has been conducted in other laboratories however, and figures from an investigation in the rat showed a spread of 0.5-1mm when 0.5µl muscimol was infused via cannula into the dorsomedial PFC and basolateral amygdala at a rate of 0.25µg/min (Allen et al. 2008), i.e the same infusion rate and volumes used in this experiment. Differences between species, brain area, and muscimol composition (fluorophore-conjugated muscimol molecules were used in the Allen et al. 2008 study) could of course cause slight differences to the present investigation, but 0.5-1mm serves as a useful estimate of the expected spread of muscimol around the infusion site.

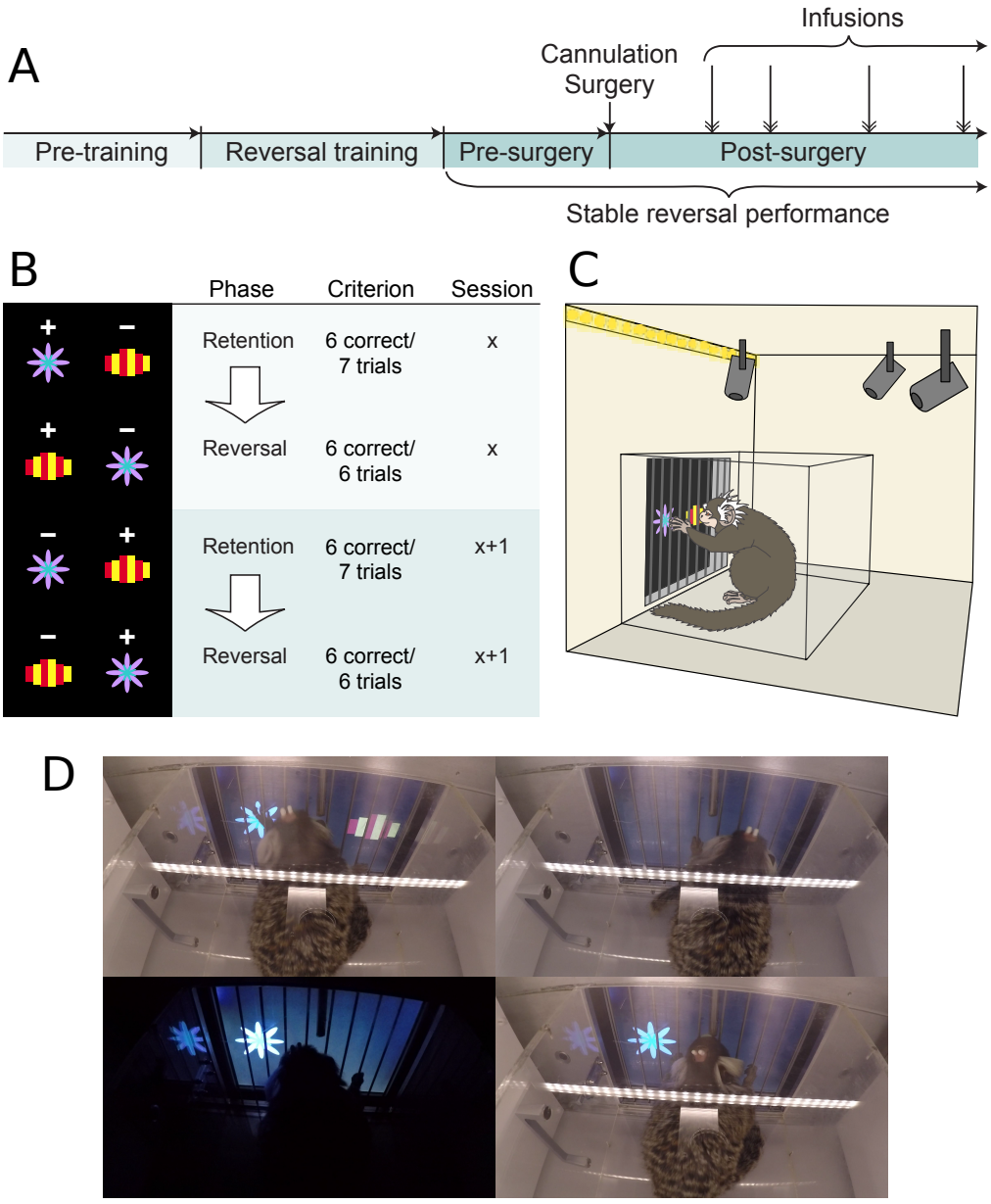

Figure 4.2.1. *Serial reversal learning paradigm task design. A. Timeline of experimental protocol. Naïve marmosets were taught to respond on the touchscreen "Pretraining", and then to perform the serial reversal learning task "Reversal training". Once marmosets were exhibiting stable reversal performance they underwent cannulation of the ventromedial caudate and putamen. Post-surgery, marmosets received intra-striatal infusions of the $GABA_A$ agonist muscimol before probe sessions, performance during which was compared to performance during infusion-free sessions of the days immediately preceding the intra-striatal muscimol probe sessions, and to sessions following intra-striatal saline administration. B. Schema illustrating stimulus-outcome contingencies across two consecutive days. After reaching a behavioural criterion of six correct responses within seven trials in the baseline discrimination phase of a session, the stimulus-outcome contingencies would be reversed, and the marmoset would then have to achieve six correct responses within six trials to pass the reversal phase of the session. The next day, the stimulus-outcome contingencies of the retention phase would be the same as those in the reversal phase of the previous day. C. Diagram illustrating the position of the marmosets within the behavioural testing apparatus and carrying box in relation to the touchscreen, houselights and video cameras. D. Photographs of a marmoset performing the serial reversal learning task, showing clockwise from top left: the marmoset touching a stimulus, an inter-trial interval, collection of banana milkshake reward following a response to the correct stimulus, and punishment darkness following a response to the incorrect stimulus.*

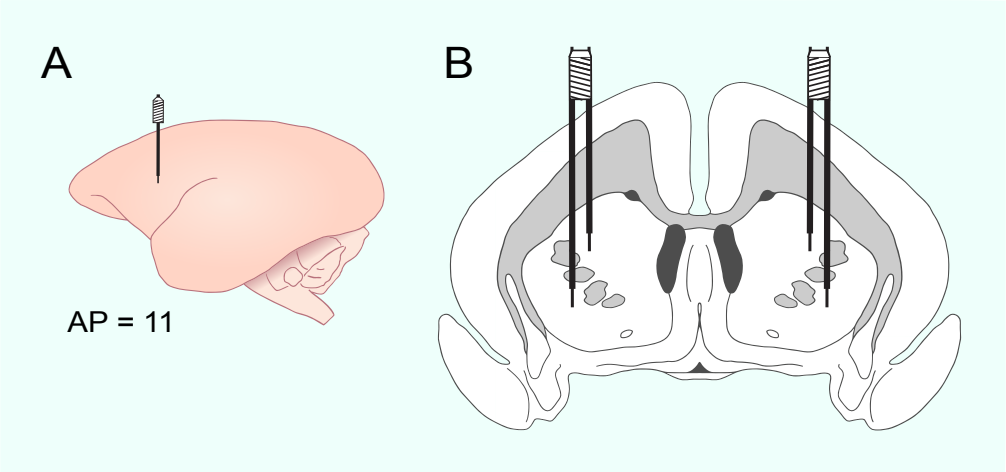

Figure 4.2.2. *Schematic diagram showing position of cannulae targeting the ventromedial caudate and anterior putamen. A. Side view of cannulae. B. Cannulae shown against a coronal section in the 11 AP plane; medial guide targets caudate and lateral guide the putamen.*

4.2.4 Statistical analyses

Intra-putamen muscimol inactivation data were analysed using mixed model ANOVAs, which were programmed using the statistical computing language R, version 3.3.1 with the Mac GUI R.app version 1.68 (R Core Team 2016). Linear mixed-effects modelling was achieved with the lme4 package (Bates et al. 2015), with statistical tests applied with the lmerTest package (Kuznetsova et al. 2016) using Type III sums of squares with the Satterthwaite approximation for degrees of freedom. Data from muscimol infusion sessions were compared against data from two different control conditions:

1. sessions in which saline, as opposed to muscimol, was infused into the putamen
2. sessions of the days immediately preceding intra-putamen muscimol infusions, where no infusions occurred

The dependent variable used was a difference score, calculated by taking the number of errors made in a phase (baseline discrimination or reversal) of a session in which the subject received an infusion (muscimol or saline), and subtracting from it the number of errors made in the phase of the session on the preceding day, where no infusions occurred. ANOVA analysis was performed for the putamen and caudate inactivation separately, given insufficient data to analyse the entire dataset at once. Fixed factors chosen for the initial ANOVA analyses included the phase of session, i.e. baseline discrimination or reversal ("Phase"), and the dose of muscimol or alternatively saline administration ("Dose"), while subject was modelled as a random factor. Further analysis of subsets of the data was subsequently performed separately following the finding of a significant Phase*Dose interactions, with separate mixed-model ANOVAs performed on the baseline discrimination and the reversal data. Post hoc pairwise comparisons were made between individual data points based on the estimated marginal means with the Bonferroni-Holm adjustment.

Due to inter-individual variation in the specific doses which elicited differential effects, for each animal the "high", "intermediate" and "low" muscimol dose effects mapped to a slightly different range of doses. The doses given were therefore categorised as "High", "Intermediate" and "Low" respectively per subject for the purposes of statistical analysis. Descriptive statistics were computed using the plyr package (Wickham 2011). All statistical values are quoted to three significant figures.

4.3 Results

4.3.1 Cannula placement assessment

As can be seen in Figure 4.3.1, the tracts left by the cannulae give evidence that the placement of the cannulae was as planned (Figure 4.2.2), and the vm caudate and central putamen were successfully targeted for all four subjects. There was some variation in the positioning of the cannulae along the AP axis, with the positioning of Subjects 2a and 2d best shown at AP 11.4, and the positioning of Subjects 2b and 2c best shown at 10.6.

4.3.2 Intra-putamen muscimol infusion selectively and dose-dependently impaired serial reversal learning

Inactivation of the putamen via the infusion of muscimol induced graded, dose-dependent deficits specific to the reversal phase of the task. However, there were individual differences in the effectiveness of muscimol doses across subjects, thus necessitating an operational categorisation of doses into "Low", "Intermediate" and "High", as already described (§4.2.4).

Thus, considering Table 4.2, it can be seen that the pattern of effects was consistent across these dosing categories from no deficit for the lowest dose range (0.03-0.1μg), to a reversal-specific deficit in the intermediate range (0.06-0.3μg), to more profound deficits at the highest dose range (0.1-0.3μg). In fact, performance was so severely disrupted at the "High" dose, that all three subjects failed to complete the reversal phase of the task. Therefore, a mixed model ANOVA was conducted using the error difference score as the dependent variable, in which only "Intermediate" and "Low" dosing categories as well as "Saline" were included. There was a significant Phase*Dose interaction ($F(2,16) = 6.03$; $p < 0.05$). Subsequent analysis of the two phases of the experiment separately showed that intra-putamen muscimol did not affect the baseline discrimination phase ($F(2,4.94) = 1.06$; $p = 0.414$), but did produce a significant deficit in the reversal phase ($F(2,8) = 5.05$; $p < 0.05$), such that the Middle dose of muscimol caused subjects to commit significantly more errors compared to Saline or the Low dose (pairwise comparisons: Middle vs Saline: [$p < 0.05$], Middle vs Low: [$p < 0.05$]). Performance after receiving the Low dose of intra-putamen muscimol did not differ from performance after receiving intra-putamen saline ($p = 0.903$).

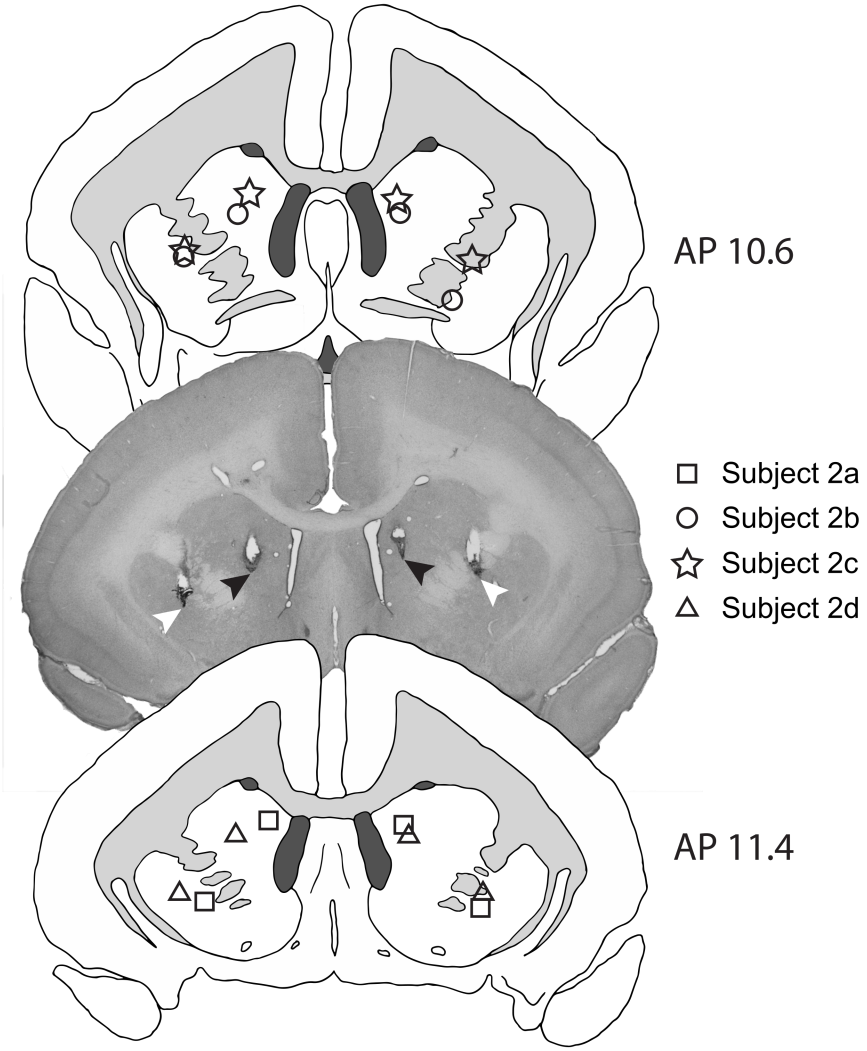

Figure 4.3.1. *Schematics and representative histological section (taken from Subject 2c) showing the intracerebral cannulae placement in the vm caudate and putamen for each subject, in AP planes 10.6 or 11.4. In the histological section, black arrows show the placement of the ventromedial caudate cannulae, and white arrows the placement of the putamen cannulae.*

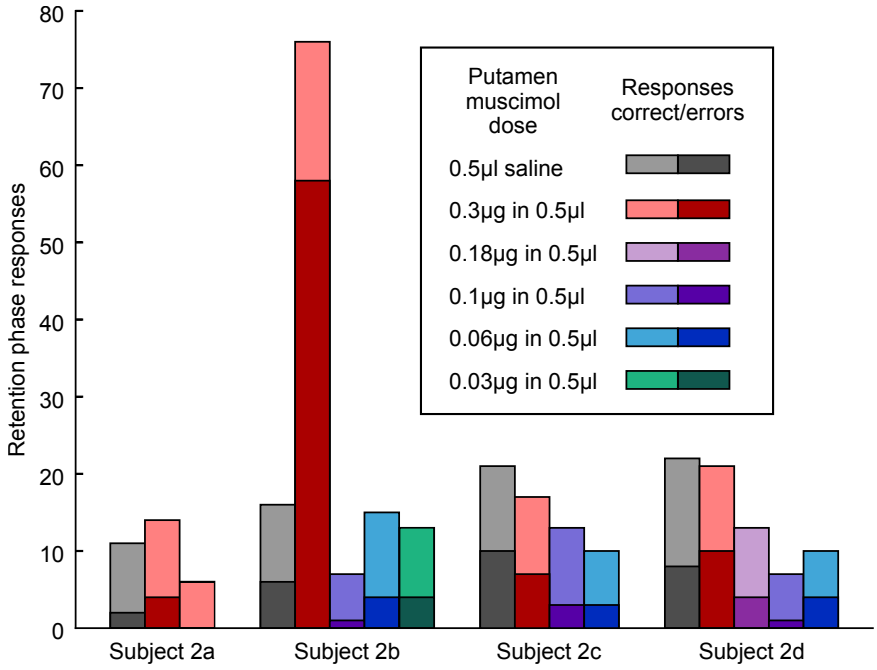

Figure 4.3.2. *Responses in the retention phase at each putamen muscimol dose and following saline administration per animal, showing numbers of correct responses and errors.*

Table 4.2. *Doses of muscimol infused into the putamen and caudate*

	Intra-cerebral doses of muscimol per region (µg)											
	Putamen						Caudate					
Subject	0.01	0.03	0.06	0.1	0.18	0.3	0.01	0.03	0.06	0.1	0.18	0.3
Subject 2a						x						x
Subject 2b	x	x	x				x	x	x			
Subject 2c			x	x		x		x		x		x
Subject 2d				x	x	x					x	x

x denotes doses given to each subject;

4.3.2.1 Intra-putamen muscimol did not affect retention of stimulus/action-outcome contingencies

Parallel analyses revealed that intra-putamen muscimol did not affect performance of marmosets in the baseline discrimination phase of the task ($F(2,4.94) = 1.06$; $p = 0.414$). The performance of the marmosets in the baseline discrimination phase under intra-putamen muscimol and saline infusion is displayed graphically in Figure 4.3.2.

4.3.2.2 Intra-putamen muscimol dose-dependently impaired reversal learning

Administration of muscimol into the putamen induced dose-dependent deficits in the reversal phase of the task. At the lowest doses, the monkeys displayed little to no impairment. At the highest doses, subjects exhibited the most profound impairments whereby they never reached the task criterion of six consecutive correct responses, thus failing the reversal phase of the session. At lower, intermediate doses, they

tended to show a subtler form of impairment where they performed more errors in responding but often nevertheless eventually reached the learning criterion for the reversal phase. These impairments are represented graphically by plotting cumulative errors against trials in the reversal phase to form learning curves (Figure 4.3.3). The gradient of the learning curve for the intermediate doses tended to be steeper than that for the equivalent curve of the saline session, indicative of commission of a higher proportion of errors.

The behavioural responses of the marmosets to the different doses of muscimol were characterised by inter-individual differences. For example, at the highest dose of 0.3µg muscimol in 0.5µl saline Subject 2c failed the reversal phase of the session, showing a profound degree of impairment similar to that seen in the other subjects. However, while the other subjects tended to continue to perform trials throughout the session and still failed, Subject 2c's responding declined over the session, resulting in a reduced number of trials performed overall at the 0.3µg dose, and designated a "truncated failure". Moreover, another subject Subject 2c showed a unique behavioural response at the 0.1µg muscimol in 0.5µl saline dose. He failed to reach the behavioural criterion and did not pass the reversal phase of the session, in common with the deficits shown by the other subjects at similar doses, but also displayed a perseverative licking behaviour which was overlaid on his responding. After receiving reward he continued to lick the milkshake delivery spout for several seconds after milkshake delivery had ceased, before recommencing responding, an idiosyncratic behaviour not seen at any other dose nor in any other subject.

While the profile of dose-dependent effects was consistent across subjects[1], there was inter-individual variation in the specific doses which elicited the differential effects; for each animal the "high", "middle" and "low" effects mapped to a slightly different range of doses. The doses given were therefore catergorised as "High", "Middle" and "Low" respectively per subject for the purposes of statistical analysis (Table 4.3).

Table 4.3. *Classification of intra-putamen muscimol doses as high, middle and low effectors by subject.*

	Subjects			
Dose	Subject 2a	Subject 2b	Subject 2c	Subject 2d
High	0.3µg	0.1µg	0.3µg	0.3µg
Middle		0.06µg	0.1µg	0.18µg
Low		0.03µg	0.06µg	0.1µg

4.3.3 Intra-caudate muscimol infusion impaired general discrimination learning

Inactivation of the caudate via the infusion of muscimol induced impairments across both the baseline discrimination and reversal phases of the task, that were again graded and dose-dependent. As with the intra-putamen muscimol infusions, the individual variability in effectiveness of the muscimol doses meant that they were categorised as 'Low', 'Intermediate' and 'High', as shown in Table 4.4.

[1] One subject, Subject 2a, unfortunately only received one dose of muscimol, 0.3µg muscimol in 0.5µl saline (though this dose was given twice and its effect replicated). Subject 2a was the first subject chronologically to enter the study, and was euthanased following the development of a crack in the dental cement securing his striatal cannulae. The crack did not appear to have any adverse effects on Subject 2a behaviourally, and there were no negative welfare indicators, but it was judged that it increased his risk of developing a more serious problem with the cannulae and so euthanasia was deemed prudent. At that point in time, the other subjects were still in training and the dose-dependency of the deficits induced by intra-putamen muscimol was not yet known, and so he was not tested with any lower doses.

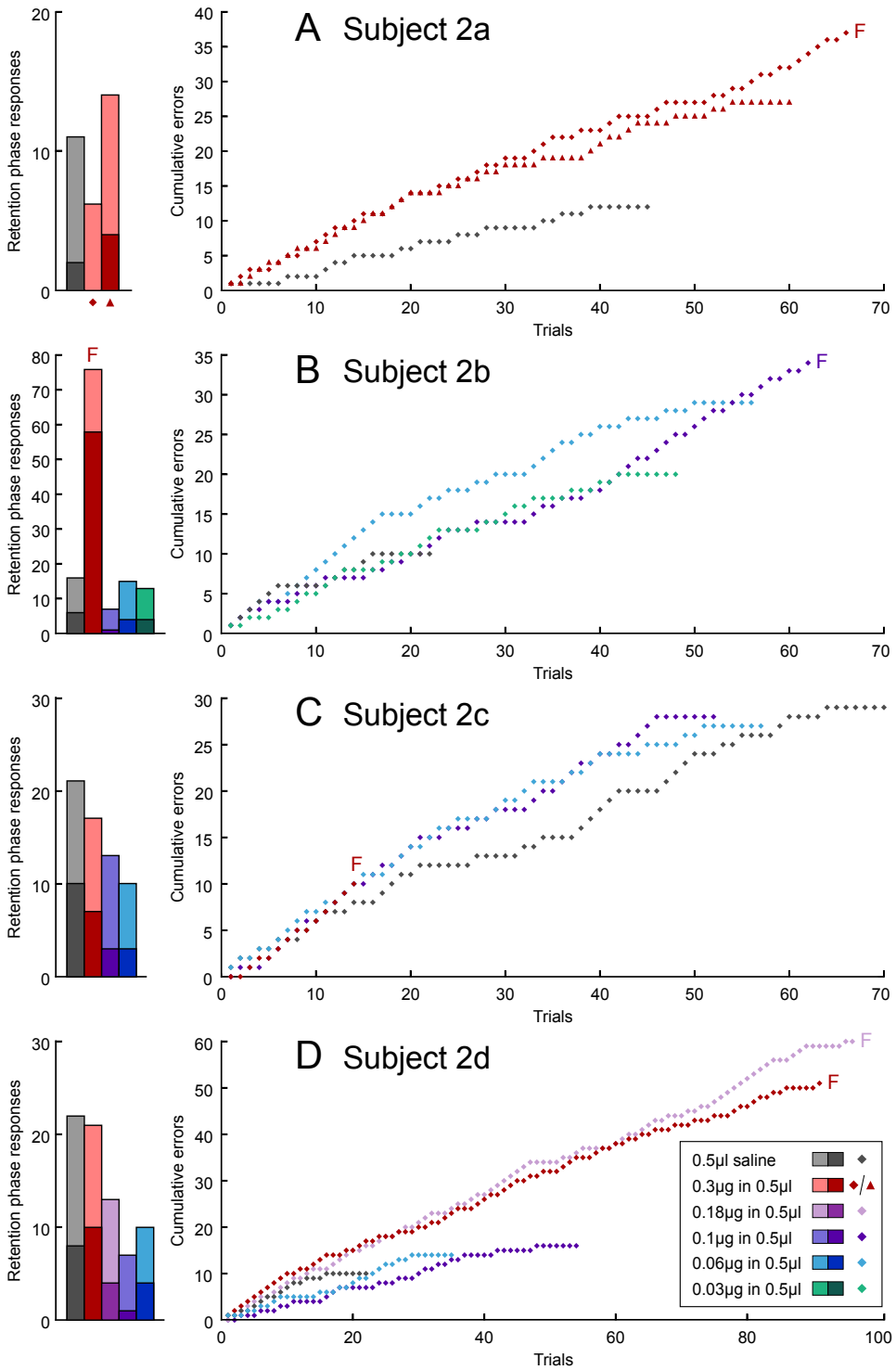

Figure 4.3.3. *Effects of intra-putamen administration of muscimol and saline on the retention and reversal phases of the task per subject. Retention phase performance displayed as bar graphs giving the total number of responses in the retention phase, split into correct (light shading) and incorrect trials/errors (dark shading). Reversal phase performance is shown as a learning curve, with cumulative errors plotted against trials. F denotes the failure of a subject to pass the relevant phase at a specific dose. In panel A, showing the data from Subject 2a, the data from original administration of 0.3µg dose is shown, as well as data from the replication of the 0.3µg dose, represented with diamonds and triangles respectively.*

Table 4.4. Classification of intra-caudate muscimol doses as high, middle and low effectors by subject.

	Subjects			
Dose	Subject 2a	Subject 2b	Subject 2c	Subject 2d
High		0.06µg	0.3µg	0.3µg
Middle		0.03µg	0.1µg	
Low	0.3µg	0.01µg	0.03µg	0.18µg

A mixed model ANOVA was conducted using the error difference score as the dependent variable. There was a significant Phase*Dose interaction ($F(3,16) = 3.44$; $p < 0.05$) and a main effect of Dose ($F(3,16) = 13.4$; $p < 0.001$). Subsequent analysis of the two phases of the experiment separately showed that intra-caudate muscimol produced a significant deficit in the baseline discrimination phase ($F(3,9) = 8.99$; $p < 0.005$), such that the High dose of muscimol caused subjects to commit significantly more errors than Saline or the Low dose of muscimol (pairwise comparisons: High vs Saline: [$p < 0.0005$], High vs Low: [$p < 0.0005$]). There was also a trend level difference between the performance following intra caudate infusion of the High and Middle doses ($p = 0.0612$). There were no significant differences between the performance following the other dosing categories, i.e. Low vs Saline ($p = 1$), Middle vs Saline ($p = 0.409$), Middle vs Low ($p = 0.409$).

Mixed model ANOVA of the intra-caudate muscimol data for the reversal phase showed a main effect of Dose ($F(3,7) = 8.04$; $p < 0.05$). Post hoc pairwise comparisons suggested that the subjects commited fewer errors when in receipt of the Low dose of intra-caudate muscimol, compared to the saline ($p < 0.005$), and the High ($p < 0.0005$) and Middle ($p < 0.005$) doses of muscimol. No other comparisons were significant (High vs Saline: [$p = 0.444$], High vs Middle: [$p = 0.641$], Middle vs Saline: [$p = 0.444$]). When in receipt of the Low and Middle doses of intra-caudate muscimol, Subject 2b did not reach the behavioural criterion of six correct response within seven trials to progress to the reversal phase of the task, and so did not contribute data points for those dosing categories in the reversal phase.

4.4 Discussion

Intra-putamen muscimol administration impaired performance in a serial reversal learning task in the marmoset. The impairment was selective to the reversal phase of the task; performance in the retention phase of the task was unchanged. The impairment was also dose-dependent; at higher doses subjects showed the most profound deficits, more subtle deficits at medium doses and little to no deficit at low doses. Dose-response curves were of this same general pattern for all subjects, but there were high individual differences between subjects in dose responsiveness; e.g. a high, behaviourally disruptive dose for one animal was ineffective in another.

Intra-caudate muscimol administration also impaired performance in the serial reversal learning task. In the baseline discrimination phase of the task, the pattern of the impairments was similar to that seen in the intra-putamen muscimol data for the reversal phase: there was a graded, dose-dependent deficit whereby subjects committed the most errors at the highest doses. Surprisingly, analysis of the reversal phase under intra-caudate muscimol then suggested that performance here too was being significantly affected, but that the statistical difference was driven by subjects committing fewer errors when in receipt of their low dose of muscimol. More likely than a paradoxical improvement in performance at low doses of intra-caudate muscimol is that performance was simply extremely variable, and that the result is anomalous.

Subjects were generally impaired in their discriminative capabilities, as exhibited in their graded, dose-dependent deficits during the baseline discrimination phase, and by the time they entered the reversal phase of the task were behaving erratically. There were also fewer data points that could be included in the analysis of the intra-caudate muscimol reversal phase data set.

The serial reversal learning paradigm was selected for use in the present investigation as it facilitates the application of multiple acute manipulations. At the core of the paradigm is the development of a stable level of reversal learning performance for each subject, stable performance which can then be used as a baseline against which acute manipulations can be compared. Such a design dramatically reduces the number of animals needed for the experiments, in line with the "3Rs" principles of replacement, reduction and refinement promoted for humane animal research (Russell and Burch 1959; National Centre for the Replacement Refinement and Reduction of Animals in Research (NC3Rs) 2016).

Another key advantage of the experimental design is the daily retention phase where subjects are tested on the previous day's response-outcome contingencies. The term "retention" may be a misnomer, as the extensive reversal history in similar serial reversal paradigms has been suggested to induce proactive interference (Underwood 1957; Keppel and Underwood 1962), and thus make it easier for animals to lose track of the contingencies that were in place the previous day (Gonzalez et al. 1966; 1967; Mackintosh et al. 1968; Mackintosh and Little 1969). Nevertheless, the retention phase of the task serves as a useful control during manipulations; if a subject can successfully discriminate between the stimuli in the retention phase, any deficits seen in reversal performance must be selective to the reversal itself, and not due to difficulties in any other realm such as discriminative capabilities, attention or motivation.

Primates have long been known to form learning sets over the course of training in the solution of discrimination problems (Harlow 1949; Levinson and Reese 1967; Schrier and Povar 1978; Gaffan 1985; Washburn and Rumbaugh 1991; Yokoyama et al. 2004; Browning et al. 2007). The formation of a learning set can be described as the learning of how to learn to solve a certain type of problem while committing the fewest errors, and as such substantially helps to optimise performance, as evidenced by an increase in the learning rate over successive problems (Harlow 1949). There is also support in the literature for the formation of *reversal learning sets* over successive reversal problems involving fresh discriminative pairs (Harlow 1949; Meyer 1951) and in serial reversals involving the same pair of stimuli (Warren 1966; Gaffan and Harrison 1984; Gaffan 1985; Rygula et al. 2010). The development of learning sets has been demonstrated in marmoset monkeys specifically across discrimination problems, reversal learning problems and in serial reversal learning (Miles and Meyer 1956; Cotterman et al. 1956; Rygula et al. 2010). It has been theorised that monkeys develop a win-stay/lose-shift strategy as part of their reversal learning set (Schusterman 1962; Warren 1966), but this does not appear to contribute to the progressive improvements in reversal learning performance seen in animals such as cats, rats and pigeons (Warren 1966; Mackintosh et al. 1968; Mackintosh and Little 1969; Reid and Morris 1992).

The need for the development of a stable baseline of serial reversal performance necessitated extensive training of the task before cannulation surgery and muscimol infusion. Subjects were thus substantially overtrained on the task at the point of data collection. Overtraining is known to engender a shift to habitual, rather than goal-directed, control of behaviour (Adams and Dickinson 1981a; Adams and Dickin-

son 1981b; DeRusso et al. 2010; Smith and Graybiel 2013), and thus it seems likely that behavioural routines used in the performance of the task were supported as habits. That intra-putamen muscimol infusion impaired reversal learning performance fits with an habitual mode of behaviour; the striatum has long been thought to mediate habits (Mishkin and Appenzeller 1987; Packard and Knowlton 2002; Graybiel 2008; Graybiel and Grafton 2015) and the putamen in particular has been identified as the critical locus in non-human primates (Miyachi et al. 1997; 2002; Fernandez-Ruiz et al. 2001; Deffains et al. 2010 but see Desmurget and Turner 2010).

The control of behaviour by the goal-directed and habitual systems has been discussed in the literature in relation to the formation of a learning set. Firstly, it has been shown that the magnitude of reward modulates the progressive improvement in performance seen in serial reversal learning (Feldman 1968), thus suggesting that behaviour at the time of learning set formation is goal-directed. Secondly, it has been suggested that the lateral PFC acts to inhibit the putamen, and to suppress its mediation of habitual learning during the formation of a learning set (Yokoyama et al. 2005). Taken together, these results can be used to put forward a neuropsychological timeline for the serial reversal task. In the initial stages of the task, subjects respond in a goal-directed fashion and build a reversal learning set, with responding at this stage mediated by the caudate and associative portions of the putamen. Over time, with more experience of the task and once the learning set has been formed, the lateral PFC disinhibits the putamen, removing its habit suppression, and subjects' responding becomes more habitual. Responding would, at the later stages of the task, be mostly dependent upon the sensorimotor portions of the putamen, a finding which is in line with the impairments seen following the infusion of intra-putamen muscimol.

Such a theory can partially help to resolve the apparently conflicting data from Clarke et al. 2011 and Groman et al. 2013, groups which linked the ventromedial caudate and the putamen respectively to reversal learning. At a glance, the data from the present investigation highlight a role for the putamen and thus are more allied with those of Groman et al. 2013. However, if one accepts the previously discussed reasoning of a shift in striatal contribution from the caudate to the putamen as the control of the task moves from being goal-directed to habitual, one would expect the caudate to be involved in the Clarke et al. 2011 study, in which reversal learning was tested in acquisition, but the putamen instead to contribute to the present overtrained task, in which case the results are entirely compatible. A problem with such reasoning is that in the paradigm used by Groman et al. 2013, reversal learning does not appear to be overtrained, as monkeys were given three novel discrimination problems and their reversal learning related to these problems tested in acquisition in a similar fashion to those in Clarke et al. 2011, and thus one might have predicted that the caudate would also be identified as a locus for reversal learning in that study. If anything, the Clarke et al. 2011 paradigm could be theorised to be more likely to induce habitual control than that of Groman et al. 2013, as marmosets were given a discriminative set and the response-outcome contingencies for that set reversed back and forth seven times, whereas the monkeys of Groman et al. 2013 were moved to a fresh discriminative set after reaching the behavioural criterion to pass just one reversal per set. The putamen result in Groman et al. 2013 is further supported by another result from the same group in which it was found that greater D_2-like dopamine receptor availability in both the caudate and putamen was associated with better reversal learning performance; in that investigation the paradigm was of the same structure and thus reversal learning was also tested in acquisition, and the result held when

the data was combined across all reversals including even the very first reversal (Groman et al. 2011). An alternative explanation is that inter-species differences could underlie the conflicting findings; vervet monkeys were the subjects of the Groman et al. 2011 and Groman et al. 2013 studies whilst marmosets were the subjects of the present investigation as well as the Clarke et al. 2011 study. The previous work linking the putamen to habitual control in non-human primates was carried out in two further monkey species: rhesus and crab-eating macaques (Miyachi et al. 1997; 2002; Fernandez-Ruiz et al. 2001; Deffains et al. 2010).

5 The role of the OFC and pgACC in goal-directed actions as assessed by contingency degradation

5.1 Introduction

There are two mechanisms by which instrumental behaviour is controlled: goal-directed actions and the habitual system. Goal-directed actions have been shown to depend upon the contingent relationship between actions and outcomes, while habitual behaviour, being instead concerned with stimulus–response associations, operates independently of contingent relationships. Contingency degradation is a paradigm in which this action–outcome contingent relationship is purposefully weakened by the experimenter, and therefore, in the event that an instrumental behaviour is being performed under the control of the goal-directed action and not the habitual system, has the effect of reducing the performance of said behaviour.

Whilst a number of behavioural paradigms involve the alteration of action–outcome contingencies, contingency degradation offers a tightly controlled and focused view of an animal's response to a change in contingency, without the addition of other confounding variables. Despite being a task with great translational potential, it remains relatively understudied compared to more popular paradigms of changing action–outcome contingency such as reversal learning, or the other hallmark test of goal–directed action, outcome revaluation. It is therefore unsurprising that our understanding of how the PFC mediates sensitivity to contingency degradation, and in particular which subregions control which aspects of contingency learning, is still unclear.

The medial prefrontal cortex was first implicated in behavioural sensitivity to contingency degradation in a seminal study employing a pre-training lesion of the rat prelimbic cortex (Balleine and Dickinson 1998a). However, there is confusion over which region of the primate PFC acts as the functional homologue of the rodent PL (Myers-Schulz and Koenigs 2012): anterior vmPFC, dorsal ACC or pgACC are candidate regions indicated by literatures in human contingency degradation neuroimaging (Balleine and O'Doherty 2010), conditioned fear studies (Milad and Quirk 2012), and comparative anatomy respectively (Gabbott et al. 2003; Vogt et al. 2013).

Meanwhile, evidence for the role of the OFC in goal-directed actions has mostly stemmed from investigations using not contingency degradation, but the related, and more widely used, paradigm of outcome revaluation (§1.4.3.3). The few studies that have tried to identify the role of the OFC in sensitivity to contingency degradation have yielded conflicting results. Lesions of the medial OFC were found to affect

sensitivity to contingency degradation in one study (Gourley et al. 2010), but not another (Bradfield et al. 2015), while large lesions of ventral and lateral OFC in rats disrupted behavioural sensitivity to the degradation of stimulus-outcome contingencies, though action-outcome contingency degradation was not studied (Ostlund and Balleine 2007).

In a recent study from my laboratory, it was reported that excitotoxic lesions of the OFC (areas 11 and 13, extending into area 14) or the pgACC (area 32) induced impairments in sensitivity to contingency degradation in marmosets (Jackson et al. 2016; Figure 5.1.1). The finding advanced our understanding of these regions in contingency degradation, and on a broader scale our understanding of goal-directed action in general, but left several questions still open to debate. The use of two distinct stimuli each of which were linked to each of the action–outcome pairings meant that it was difficult to tell if the poor performance of the OFC– and pgACC–lesioned marmosets stemmed from deficits in the use of stimulus– or action–outcome associations. Studies of outcome revaluation have suffered from a similar lack of specificity as two different stimuli are also used as standard in most instrumental outcome revaluation experiments in non-human primates (Málková et al. 1997; Thornton et al. 1998; Baxter et al. 2000; Izquierdo and Murray 2004; Izquierdo et al. 2004; Machado and Bachevalier 2007a; b; Baxter et al. 2009; West et al. 2011) with the notable exception of Rhodes and Murray 2013.

In the current study, the findings of Jackson et al. 2016 were built upon in a new paradigm, which as well as linking a single stimulus to both action–outcome pairings in order to limit the influence of stimulus–outcome associations on behaviour, was completely re-designed to allow multiple acute manipulations of different brain regions in the same subjects.

5.2 Methods

5.2.1 Contingency degradation task

Five common marmosets, 4 female and 1 male, took part in the study. The task used was based on that described in Jackson et al. 2016, itself modelled on the rodent paradigms of Hammond 1980 and Balleine and Dickinson 1998a, but was adapted to allow repeated, acute manipulations. After undergoing preliminary training on the touchscreen (§2.3), marmosets began to be trained on successive variable ratio (VR) schedules as detailed in Table 5.1. VR schedules were used in the training procedures as they have been shown to promote goal-directed as opposed to habitual control of behaviour (Dickinson et al. 1983; Dickinson 1985; Hilário et al. 2007; Hilario et al. 2012; Hilário and Costa 2008). In initial stages of VR training, the reward and stimulus presented were the same as those used in the preliminary touchscreen training (banana milkshake and green square respectively) but the number of times marmosets had to press in order to receive reward was steadily increased, moving from a fixed ratio (FR) 1 schedule up to VR10. Concurrently, the length of reward delivery was lengthened from 5s to 10s and marmosets were familiarised with the new rewards, blackcurrant and strawberry juice drinks, in the homecage. As the marmosets progressed through the VR schedules, the stimulus was changed to a yellow and blue "maltese cross" (Figure 5.2.1B, C and D) and rewards were changed to strawberry and blackcurrant juice (Table 5.1).

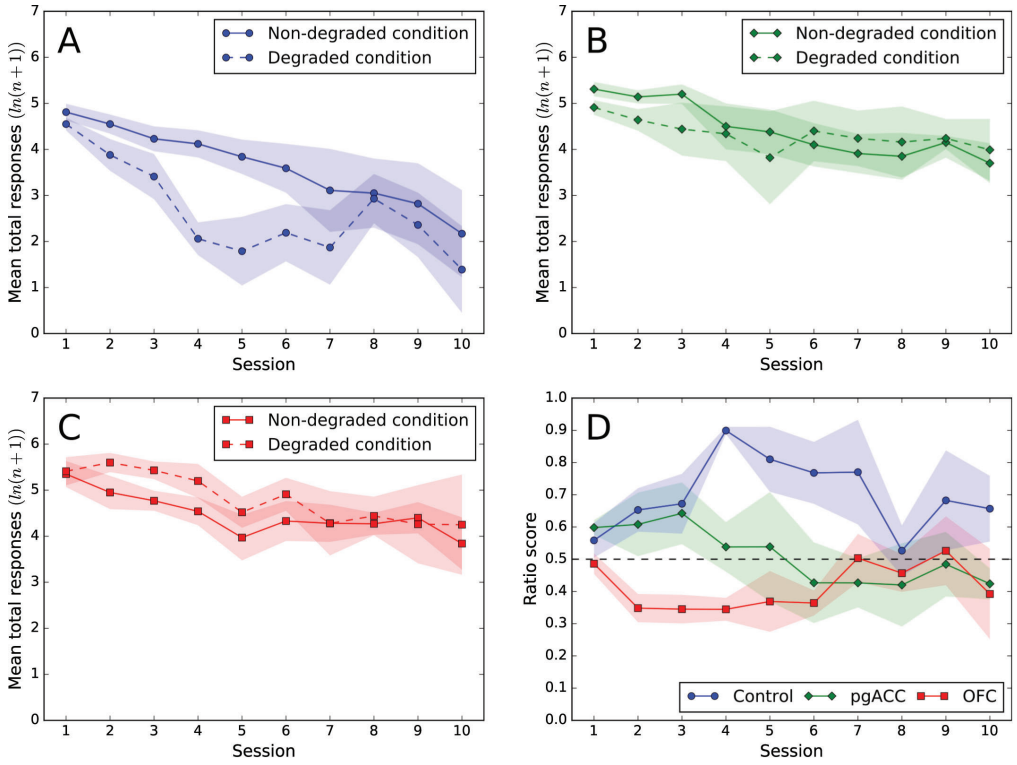

Figure 5.1.1. *Lesions of the pgACC or OFC impair sensitivity to contingency degradation in findings from Jackson et al. 2016. A-C. Mean total numbers of responses (log transformed) across sessions for each group. Responding in the degraded (dotted line) and nondegraded (solid line) conditions are shown. A. Control, n = 5. B. pgACC lesion, n = 4. C. OFC lesion, n = 5. D. Ratio scores showing mean responses normalized for the overall response rates of individual animals. The solid fill surrounding each point represents the standard error of the mean. The ratio score was calculated for each pair by dividing the number of responses in the nondegraded session by the sum of the responses from the degraded and nondegraded sessions (nondegraded/(nondegraded + degraded)). The ratio score therefore represents the proportion of responses in the nondegraded condition relative to the degraded condition with a value >0.5 indicating a greater number of responses in the nondegraded condition relative to the degraded condition.*

Movement from one training stage to the next was contingent upon marmosets consistently displaying 80 or more responses across sessions. Marmosets were always presented with only one response-outcome pairing per session, i.e. the stimulus was presented on one side of the touchscreen only, and only one type of reward was available, for the entire session. During reward availability, the birdsong cue was played, and reward receipt was dependent upon the marmoset licking the licker. They were given one testing session daily from Monday to Friday.

Following completion of the preliminary training procedures, subsequent sessions were organised, each week, into blocks of four sessions as shown in Figure 5.2.1B. Marmosets continued to be presented with one response-outcome pairing on a VR schedule per session and in the first two sessions, "Baseline 1" and "Baseline 2", there was no other opportunity for reward. However, in the third and fourth sessions of the block, the "Degraded" and "Non-degraded" sessions, a schedule of free, i.e. non-contingent, reward delivery was superimposed upon the standard response-outcome VR schedule. The type of reward, i.e. blackcurrant or strawberry juice, was the same in both sessions, and thus in one session the non-contingent reward was the same as that for which the animal could work, and in the other the non-contingent reward was not the same. In the former situation the contingency was thus partially degraded for the response-outcome pairing (in the example in Figure 5.2.1B the pairing of touching the left stimulus and receiving blackcurrant juice reward) and was therefore known as the "Degraded" session. In the latter, the only way in which the marmoset could access the reward of the standard VR schedule was by responding on the touchscreen (in the example in Figure 5.2.1B, responding to the right hand stimulus is the only way to access strawberry juice), and so the receipt of that reward was still fully contingent upon responding. The contingency of the pairing was thus not degraded at all when the contingent and non-contingent rewards were not the same, and the session was therefore known as the "Non-degraded" session.

Precise control over the degree of contingency degradation was achieved by manipulating the probabilities of contingent and non-contingent reward delivery, $P\left(O \mid A\right)$and $P\left(O \mid\sim A\right)$ respectively, which describe the probability of receiving an outcome (O) given performance of the action (A), and the probability of receiving an outcome in the absence of that action ($\sim A$). The 12 minute session was considered as a series of 1 second bins, where in each bin a response could be made or not be made. After a specified number of bins containing responses had occurred, the contingent reward was delivered. And correspondingly, after a specified number of bins had elapsed which did not contain a response, the non-contingent reward was delivered, forming two VR-like schedules. Bins in which the rewards were delivered were not counted towards either schedule and responding to the stimulus during this time had no effect. Probabilities for the two schedules, i.e. $P\left(O \mid A\right)$and $P\left(O \mid\sim A\right)$, were decided and programmed using the appropriate "VR mean". In order to prevent very small or, more problematically, very large values for the number of bins being selected, which could lead to undesirable behavioural outcomes (Bancroft and Bourret 2008), such as a marmoset becoming bored and distracted, upper and lower bounds were set which determined the maximum and minimum number of bins which could elapse before reward was given. Upper and lower bounds were symmetrical around the desired mean, and a number x was selected with uniform probability from the range $\alpha \leq x \leq \beta$, where α and β were the lower and upper bounds, and reward delivered after x bins either containing or not containing a response, for the con-

tingent and non-contingent reward schedules respectively. The schedule was thus similar to a classic VR schedule (Miltenberger 2016), but superimposed onto the bin-based structure of the session. Example probabilities, VR means and upper and lower bounds are shown in Figure 5.2.1E.

Once marmosets were exhibiting stable performance at the final stage of training, they were given probe contingency degradation sessions, as described above, in order to titrate the level of non-contingent reward delivery which would be sufficient to induce a selective suppression of responding in the degraded session. With too high a probability of non-contingent reward delivery, responding was suppressed in both the non-degraded session and the degraded session, but with too low a probability of non-contingent reward delivery responding was unchanged in both sessions. At an intermediate probability marmosets tended to maintain their normal response levels, or to decrease their responding slightly, in the non-degraded session, whilst reducing their responding in the degraded session to a much greater extent. The exact probability at which this desired behaviour manifested varied between marmosets, based upon individual differences in motivation and response rate, and thus it had to be calibrated for each subject. Probe contingency degradation sessions were tried for each subject with each juice, and one juice chosen to take forward per animal to be used in the contingency degradations at the determined probability. Marmosets tended to exhibit a slight preference for one juice over the other, and thus would be more likely to continue to respond, albeit at a reduced rate, if the response-outcome contingency involving the non-preferred juice were degraded and hence the non-preferred juice given for free. For some subjects, if the response-outcome contingency involving the preferred juice were degraded and thus the preferred juice given for free, this had an extremely suppressive effect on responding where marmosets were not willing to continue to work for the non-preferred juice. The non-preferred juice was thus the juice choses to take forward to be used in the contingency degradations.

When the probabilities to be used had been established and subjects were exhibiting stable contingency degradation performance, marmosets underwent surgery to cannulate regions of interest (see §5.2.3), and post-recovery, the regions were inactivated during contingency probe sessions.

5.2.2 Behavioural measures

Responding was analysed by taking a raw measure of performance in the Degraded and Non-degraded sessions, the total number of responses, and normalising it to the relevant baseline session of that block, i.e. the baseline session with the same contingent response–outcome schedule. This helped to control for local variation within an animal's performance over time, including for differences in performance between sessions with the preferred or non-preferred juices, and allowed comparison between animals with different baseline levels of responding. For example, in Figure 5.2.1, the Non–degraded session would be compared to Baseline 1, and the Degraded session to Baseline 2.

5.2.3 Cannulation surgeries

Though there were initially three regions of interest, the OFC, area 32 and the caudate, it was impractical to implant marmosets with cannulae targeting more than two regions and thus only two of the three regions

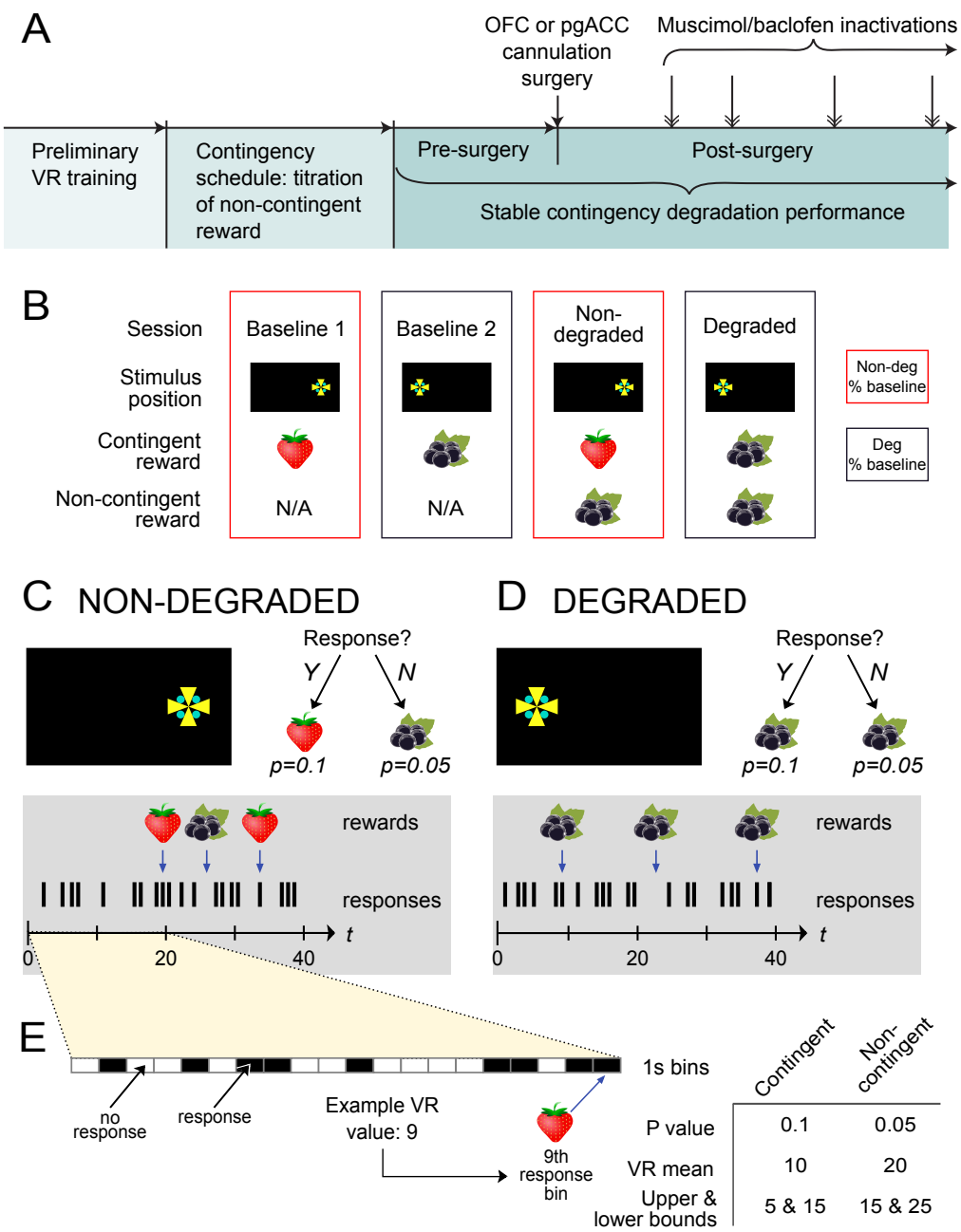

Figure 5.2.1. *Contingency task design. A. Timeline for training and task performance. B. Schema of an example degradation block comprising four sessions. Red and blue outlines denote the pairs of sessions used in normalisation. C, D. Illustration of stimuli and their relative positions on the touchscreen along with a simulated series of responses with contingent and noncontingent rewards. Action (pressing left or right) and juice pairing, probability of non-contingent reward delivery, as well as which action-outcome contingency is degraded are examples and vary between animals. E. Left. Illustration of contingent and non-contingent schedules applied using the mechanism of 1s bins. A simulated series of responses is shown as black (response) or white (no response) rectangles. For an example VR value of 9, it is shown that the 9th 1s bin containing a response induces delivery of the contingent reward. Right. Example p values, "VR" means and upper and lower bounds which would be used to program the contingent and non-contingent schedules used in this example.*

Table 5.1. *Preliminary VR training for contingency task. Mean number of sessions rounded to the nearest whole number.*

VR schedule	VR range	Stimulus	Juice	Reward length (s)	Mean number of sessions
FR1	1	Green square	Banana milkshake	5	8
VR3	2-4	Green square	Banana milkshake	5	8
VR6	4-8	Green square	Banana milkshake	7.5	10
VR10	5-15	Green square	Banana milkshake	10	18
VR10	5-15	Green square	Blackcurrant and strawberry	10	4
Jackson	5-15	Green square	Blackcurrant and strawberry	10	6
Jackson	5-15	Maltese cross	Blackcurrant and strawberry	10	10

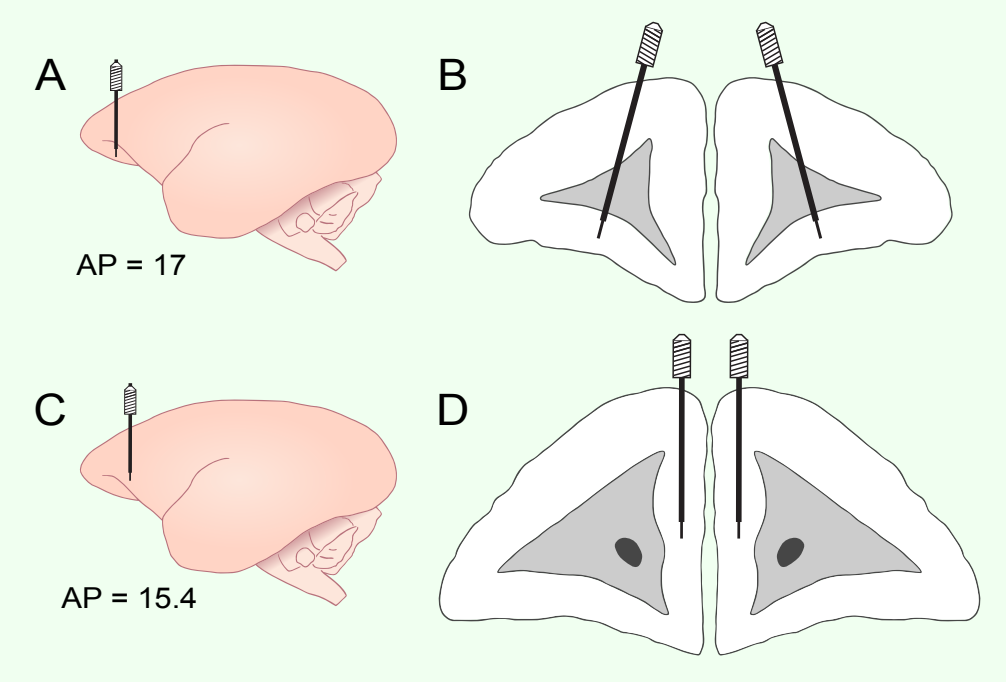

Figure 5.2.2. *Schematic diagram showing position of cannulae in animals where the OFC and area 32 were targeted. A, B. OFC cannulation. C, D. Area 32 cannulation. A, C. Side view of cannulae. B, D. Cannulae shown against coronal sections in the relevant AP plane.*

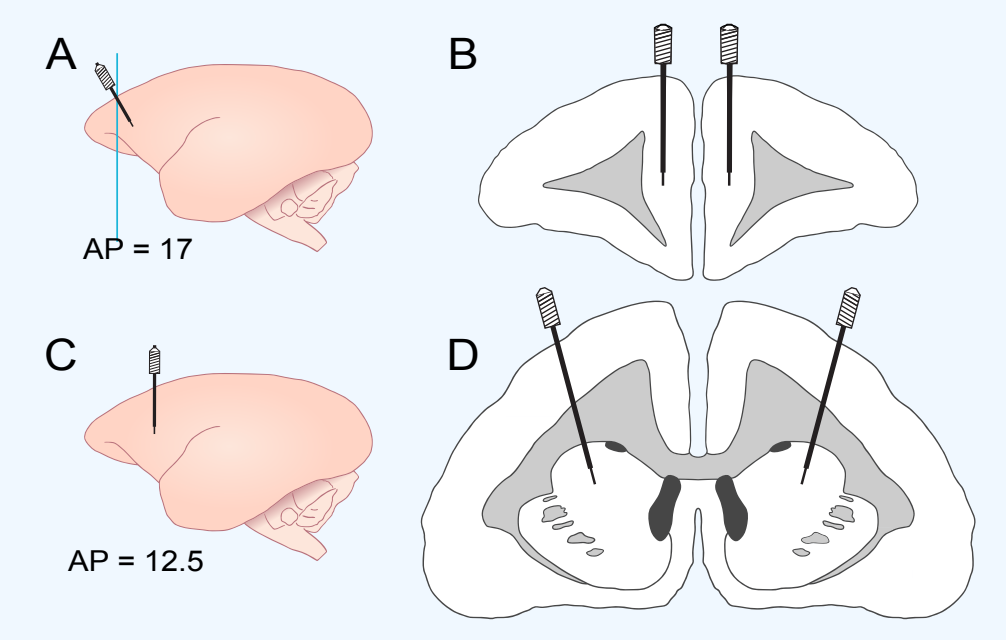

Figure 5.2.3. *Schematic diagram showing position of cannulae in animals where the area 32 and the caudate were targeted. A, B. Area 32 cannulation. C, D. Caudate cannulation. A, C. Side view of cannulae. B, D. Cannulae shown against coronal sections in the relevant AP plane.*

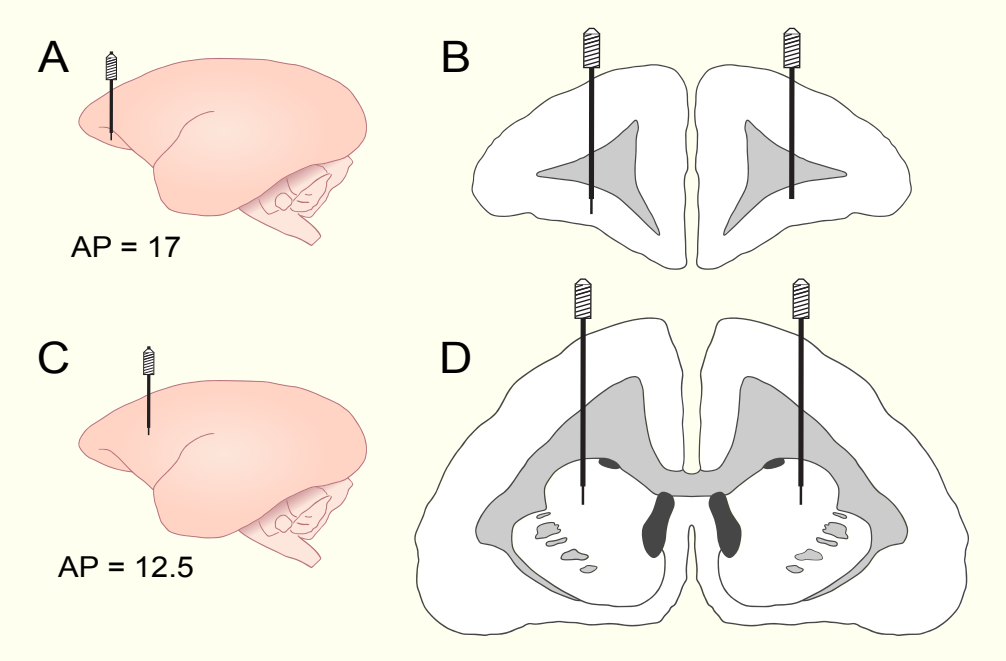

Figure 5.2.4. *Schematic diagram showing position of cannulae in animals where the OFC and caudate were targeted. A, B. OFC cannulation. C, D. Caudate cannulation. A, C. Side view of cannulae. B, D. Cannulae shown against coronal sections in the relevant AP plane.*

Table 5.2. *Orientations and AP co-ordinates of cannulae used to target the OFC, area 32 and the caudate.*

Area	Other area in combination	AP co-ordinate	Angle
OFC	Area 32	17.0	15° to midline
	Caudate	17.0	Vertical
Area 32	OFC	15.4	Vertical
	Caudate	17.0	30° to anterior
Caudate	OFC	12.5	Vertical
	Area 32	12.5	10° to lateral

were cannulated per animal. However, the angular positioning of the cannulae used to target a given region sometimes had to be changed depending on the other region co-cannulated in that animal; different combinations of areas required different spatial orientations to be used. Vertical cannula placement was always used where possible, as it was the simplest implantation and therefore gave the shortest surgery, and concomitantly the shortest time spent under anaesthesia by the animal. The orientations and AP co-ordinates used to target the regions when in combination with each other are shown in Table 5.2. Figures 5.2.2, 5.2.3 and 5.2.4 show the three possible combinations of areas and the positioning of cannulae used for each. Surgical procedures were as previously described (§2.4).

5.2.4 Intra-cerebral drug infusions

Marmosets received drug infusions with the aim of inactivating the cannulated brain regions, on the Degraded and Non-degraded sessions of a given block. In control experiments, drug and saline infusions were also given on baseline sessions. Infusion procedures were as previously described (§2.5.1). In the cortical areas, pgACC (area 32) and OFC, a cocktail of 0.1mM muscimol and 1.0mM baclofen ($GABA_A$ and $GABA_B$ agonists respectively), which had previously been shown in the laboratory to give successful regional inactivations (Clarke et al. 2015), was used. In the caudate, muscimol was used alone, based on preliminary data from striatal infusions in Chapter 4, at a concentration of 0.1µg/µl. Volumes of 0.5µl of solution were infused over 2 minutes in both cases.

5.2.5 Statistical analysis

Statistical analysis consisted of a mixed model ANOVA conducted using the statistical computing language R, version 3.3.1 with the Mac GUI R.app version 1.68 (R Core Team 2016). Linear mixed-effects modelling was achieved with the lme4 package (Bates et al. 2014), with statistical tests applied with the lmerTest package (Kuznetsova et al. 2016) using Type III sums of squares with the Satterthwaite approximation for degrees of freedom. The dependent variable used was the total number of responses in each of the degraded and non-degraded sessions as a percentage of the number of responses in the relevant baseline session in which the same action and contingent outcome was available. Fixed factors included

were infusion area ("Area"; pgACC or OFC), infusion type ("Infusion"; saline or muscimol-baclofen) and degradation condition ("Degradation Condition"; degraded or nondegraded), and subject was a random factor. Further analysis of the datasets for individual areas were subsequently performed separately following the finding of a significant three-way interaction. In each area-specific ANOVA, saline infusion data from intra-OFC and intra-pgACC infusions was pooled for those subjects that had received both, i.e. Subject 3a and Subject 3c (Table 5.3). Welch's paired t-tests were performed on the baseline control data. Descriptive statistics were computed using the plyr package (Wickham 2011). All statistical values are quoted to three significant figures.

5.3 Results

Table 5.3. *Subjects and cannulation sites included in mixed model ANOVA analysis.*

	Cannulation sites	
Subject	OFC	pgACC
Subject 3a	✓	✓
Subject 3b	✓	-
Subject 3c	✓	✓
Subject 3d	-	✓

Preliminary results from the caudate inactivations were inconsistent and thus were not followed up, and are not reported here. Subsequent histological analysis of the cannula tracts showed that for one of the animals the cannula did not reach the caudate, thus invalidating the preliminary data from the area. The OFC and pgACC datasets however are fully reported, and are awaiting histological analysis of cannula placement at the time of writing. Each of the four subjects had one of OFC, pgACC or both areas cannulated, as described in Table 5.3.

5.3.1 Noncontingent reward had a suppressive effect upon responding which was enhanced in the degraded compared to the nondegraded sessions

The delivery of non-contingent reward had a suppressive effect upon responding regardless of whether the noncontingent reward was the same or different from the contingent reward, but was greater in magnitude in the degraded compared to the non-degraded session, at a particular probability for all subjects. The probabilities and consequent "VR means" and upper and lower bounds used for each subject are shown in Table 5.4. Due to changes in levels of responding over the course of the experiment, noncontingent reward was delivered to Subject 3a with a probability of 0.02 for the pgACC infusions and with a probability of 0.03 for the OFC infusions. As can be seen in Figure 5.3.1, the response suppression effect was stable for all animals across the control contingency degradation session (the degradation immediately preceding the intra–OFC or –pgACC saline infusion contingency degradation at the equivalent probability) and the intra-OFC and/or -pgACC saline infusion contingency degradation sessions. However, despite all animals showing the same overall pattern of responding whereby responding was selectively suppressed in the degraded session of each contingency degradation block, relative to the non-degraded session, there was considerable variation in the baseline level of responding. Hence, Figure 5.3.2 shows the data in normalised form, with number of responses in the degraded and non-degraded sessions expressed as a percentage of the number of responses in the relevant baseline session in which the same action and

Table 5.4. *Subjects and probabilities, VR mean and upper and lower bounds for noncontingent reward delivery.*

Subject	Noncontingent reward delivery		
	Probability	VR mean (s)	Upper & lower bounds (s)
Subject 3c Subject 3a (pgACC)	0.02	50	45-55
Subject 3d	0.025	40	35-45
Subject 3b Subject 3a (OFC)	0.03	30	25-35

contingent outcome was available (§5.2.2). Mixed model ANOVA of percentage baseline data for intra–OFC and –pgACC saline infusion contingency degradations gave a main effect of Degradation Condition ($F_{1,4.867} = 36.0$; p=0.00202), as under saline control conditions suppression of responding in the Degraded condition was greater than in the Nondegraded condition (Degraded: 51.2 ± 21.2 < Nondegraded: 75.4 ± 16.0).

5.3.2 OFC and pgACC inactivations differentially affect behavioural response to contingency degradation

Mixed model ANOVA revealed a three-way Area x Infusion x Degradation Condition interaction ($F_{1,13.0} = 6.99$; p=0.020), which upon inspection of Figure 5.3.3, can be ascribed to the loss of differential normalised responding in the degraded and nondegraded sessions under pgACC inactivation but not OFC inactivation or saline control conditions for either area. There was a main effect of Infusion ($F_{1,13.0} = 40.7$; p=0.0000245) as the contingency degradation-induced suppression of responding was significantly attenuated under mus/bac inactivation conditions (Mus/bac: 96.1 ± 23.0 > Saline: 63.3 ± 21.9) and a main effect of Degradation Condition ($F_{1,13.0} = 13.8$; p=0.00260) as marmosets showed greater suppression of responding relative to baseline performance in the degraded condition than they did in the nondegraded session (Degraded: 70.1 ± 29.6 < Nondegraded: 89.2 ± 22.8).

5.3.3 OFC inactivation generally reduces the impact of noncontingent reward across degraded and nondegraded sessions

OFC inactivation lessened the suppressive effect of noncontingent reward delivery in both the degraded and nondegraded sessions (Figure 5.3.3A). Mixed model ANOVA of the OFC dataset correspondingly identified a main effect of Infusion ($F_{1,10.3} = 23.0$; p=0.000667). There was also a main effect of Degradation Condition ($F_{1,10.2} = 20.1$; p=0.00112), with greater suppression of responding in the degraded session than

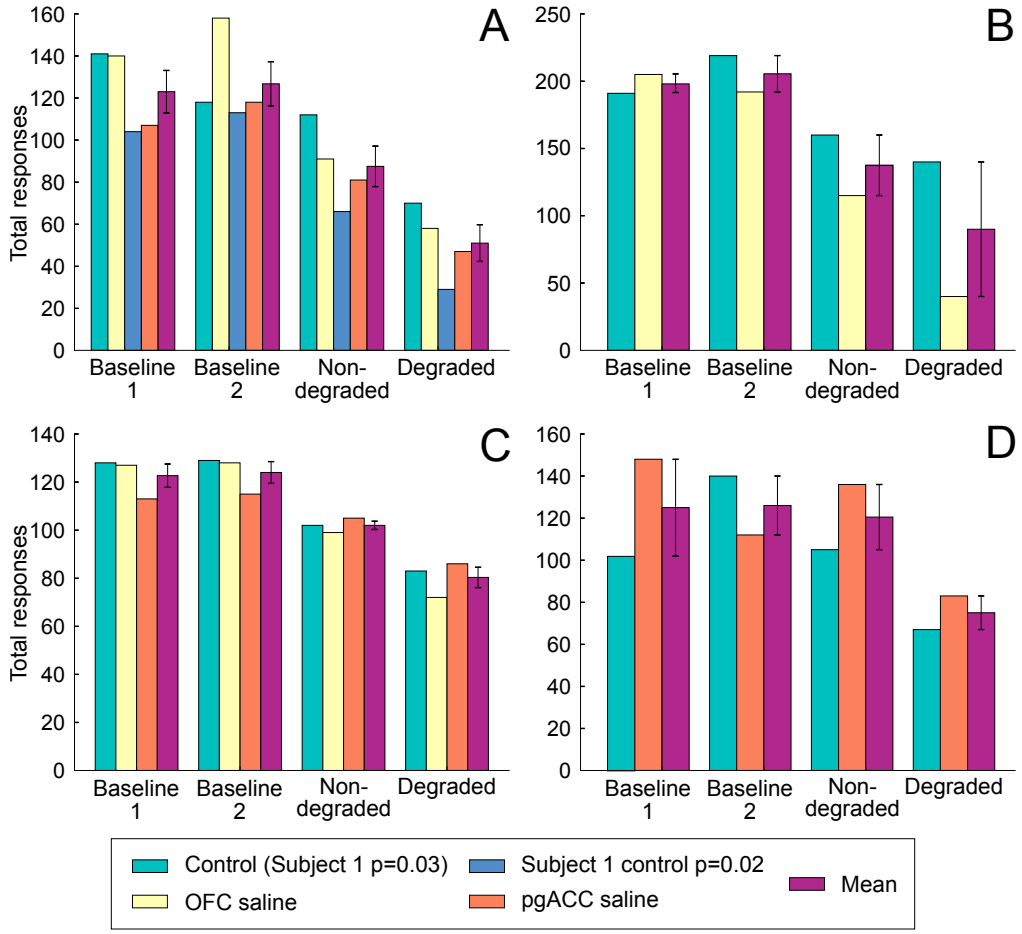

Figure 5.3.1. *Total number of responses across baseline, non-degraded and degraded sessions in the control (degradation immediately preceding the intra–OFC or –pgACC saline infusion contingency degradation at the equivalent probability) and the intra-OFC and/or intra-pgACC saline infusion contingency degradations by subject. A. Subject 3a. B. Subject 3b. C. Subject 3c. D. Subject 3d.*

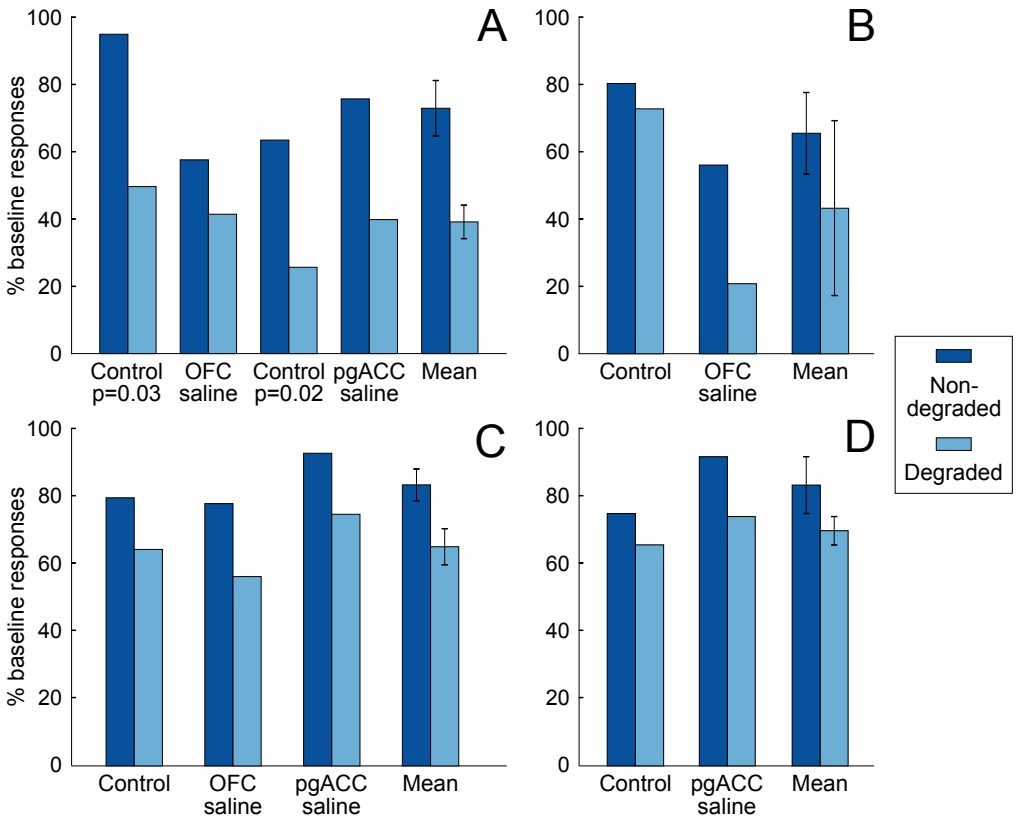

Figure 5.3.2. *Total number of responses in non-degraded and degraded sessions in the control (degradation immediately preceding the intra-OFC or pgACC saline infusion contingency degradation at the equivalent probability) and the intra-OFC and/or intra-pgACC saline infusion contingency degradations expressed as a percentage of the number of responses in the relevant baseline session in which the same action and contingent outcome was available by subject. Mean values across all contingency degradations also given per subject, with standard error of the mean. A. Subject 3a. B. Subject 3b. C. Subject 3c. D. Subject 3d.*

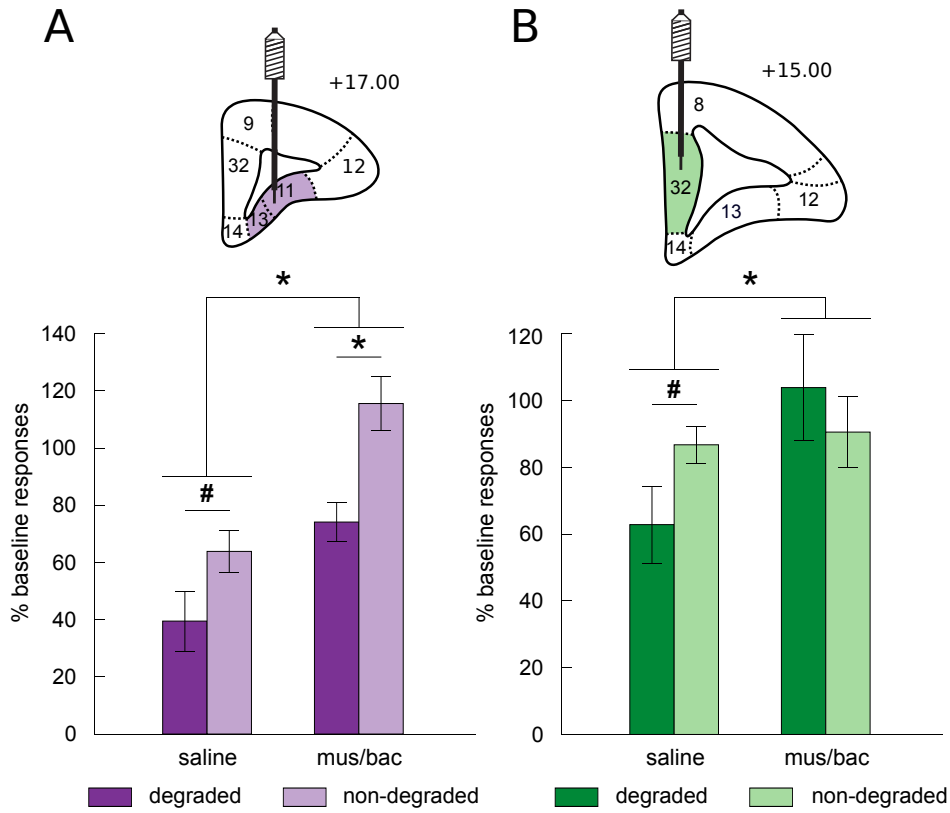

Figure 5.3.3. *Responses in degraded and nondegraded sessions expressed as a percentage of total responses in the relevant baseline session, under saline and mus/bac inactivation conditions for each area. Figures above graphs show target cannulation sites for each region. A. OFC inactivation. B. pgACC inactivation.*

in the nondegraded session (Degraded: 56.9 ± 21.8 < Nondegraded: 88.4 ± 26.7), as OFC inactivation did not influence the differential greater impact of noncontingent reward in the degraded session compared to the nondegraded session. When the intra–OFC saline and mus/bac infusion data were analysed separately there was a strong trend towards a main effect and a main effect of Degradation Condition respectively (Saline: $F_{1,2}$ = 18.4; p=0.0501. Mus/bac: $F_{1,2}$ = 112; p=0.00845).

5.3.4 *pgACC inactivation selectively alters sensitivity to specific action-outcome contingencies*

Mixed model ANOVA analysis of the pgACC dataset revealed a main effect of infusion ($F_{1,10.0}$= 23.1; p=0.000718) whereby the suppression of responding was greater under inactivation compared to the saline conditions (Mus/bac: 97.3 ± 22.1 > Saline: 68.2 ± 18.8), and an Infusion x Degradation Condition interaction ($F_{1,9.99}$ = 10.9; p=0.00809). The Infusion x Degradation Condition interaction stemmed from the loss of the differential impact of noncontingent reward delivery upon the degraded session compared to the nondegraded session under pgACC inactivation, but not in the saline control condition (Figure 5.3.3B). Separate analysis of intra–pgACC saline and mus/bac infusion data support this conclusion, with a strong trend towards a main effect of Degradation Condition in the intra-pgACC saline group ($F_{1,2}$ = 16.1; p=0.0570) but no effect in the intra-pgACC mus/bac group (p=0.371).

5.3.5 *Neither OFC nor pgACC inactivation affected responding in baseline sessions*

Intra-OFC and intra-pgACC infusions of saline and of muscimol/baclofen were given in both strawberry and blackcurrant baseline sessions in a control experiment that assessed whether inactivation of either area had any effect upon normal responding on a VR schedule (Table 5.5). Four paired Welch's t-tests (not assuming equal variances of the samples) were performed, none of which found any significant differences between conditions, comparing the following: responding during OFC inactivation and intra-OFC saline administration on the strawberry schedule (t_2 = 1.75, p=0.223), OFC inactivation and intra-OFC saline administration on the blackcurrant schedule (t_2 = 1.48, p=0.277), pgACC inactivation and intra-pgACC saline administration on the strawberry schedule (t_2 = -4, p=0.0572) and pgACC inactivation and intra-pgACC saline administration on the blackcurrant schedule (t_2 = -2.05, p=0.177).

Table 5.5. *Responding in baseline sessions under control infusions of saline and mus/bac by area and juice. Meaned averages and standard deviations across subjects given.*

		Infusion	
Area	Juice	Saline	Mus/bac
OFC	Strawberry	165 ± 46.0	183 ± 41.0
	Blackcurrant	143 ± 41.8	167 ± 19.7
pgACC	Strawberry	141 ± 37.0	136 ± 35.0
	Blackcurrant	146 ± 29.7	133 ± 35.0

5.4 Discussion

A novel contingency degradation task, in which acute manipulations can be used, has been developed and validated for the common marmoset. Marmosets were shown to exhibit behavioural sensitivity to

contingency degradation as demonstrated by a greater suppression of responding upon delivery of free reward in the degraded compared to the nondegraded session, which was stable over multiple contingency degradations. Inactivation of the OFC generally reduced the sensitivity of marmosets to the delivery of noncontingent reward in both nondegraded and degraded sessions, while pgACC inactivation selectively impaired sensitivity to the alteration of specific action–outcome contingencies as evidenced by a loss of differential suppression of responding between the degraded and nondegraded sessions.

The laboratory has previously reported the adaptation of a rat contingency degradation paradigm (Balleine and Dickinson 1998a, itself based upon Hammond 1980) for the marmoset, described in Jackson et al. 2016. Whilst the prior adaptation was a success, an aim of the present study was to update the task and design a paradigm capable of supporting the use of repeated, acute manipulations. Advantages of the new design included that within-subject comparisons could be made between muscimol/baclofen inactivation and saline control conditions as opposed to between-subject comparisons of lesion and sham groups, and that multiple brain areas could be cannulated per marmoset. Both of these factors reduced the number of animals that it was necessary to use in the experiments, which is in line with the "3Rs" principles of replacement, reduction and refinement promoted for humane animal research (Russell and Burch 1959; National Centre for the Replacement Refinement and Reduction of Animals in Research (NC3Rs) 2016). The paradigm also opens up the possibility of extending the investigation in the future with the use of a range of pharmacological agents that target specific cells and receptors.

As in Jackson et al. 2016, the new paradigm incorporated features designed to improve upon a weakness in the original, seminal work by Hammond 1980. An alternative explanation, levelled by learning theorists, of the Hammond result that animals detect and use contingency information in instrumental responding, was that the delivery of noncontingent reward could strengthen competing responses, such as approach to the reward source, thus making it impossible to conclude with certainty that the observed reduction in responding was due specifically to sensitivity to contingency degradation (Colwill and Rescorla 1986; Dickinson and Mulatero 1989; Balleine and Dickinson 1998a). The original design was consequently modified to introduce a second action-outcome pairing which is not degraded during the experiment but nevertheless occurs alongside the delivery of noncontingent reward. Any response competition induced by the presence of the noncontingent reward would be expected to affect the nondegraded action-outcome pairing to the same extent as the degraded action-outcome pairing, and so any difference in levels of responding between the two must be intrinsic to the contingency degradation itself (Colwill and Rescorla 1986; Dickinson and Mulatero 1989; Balleine and Dickinson 1998a). We concurred with this reasoning and thus built two action-outcome pairings into our paradigm, the contingency of only one of which was degraded.

A challenging part of the development of the task was that of choosing the probability of noncontingent reward delivery. Marmosets exhibited inter-individual differences in levels of baseline responding, presumably due to variation in motivation to work for and receive reward, which was controlled for by normalising the number of responses made in the non-degraded and degraded sessions against those in the corresponding baseline sessions (§5.2.2). However, they also displayed between-subject variation in the magnitude of suppression of responding following delivery of noncontingent reward. In general, too high a probability of noncontingent reward delivery and responding was silenced completely or dropped

to very low levels, and with too low a probability there was little to no impact upon responding, while at an intermediate level responding was partially suppressed, and the suppression was greater in the degraded compared to the non-degraded session. All marmosets followed this pattern overall, but the specific probability of noncontingent reward delivery which induced the "intermediate" effect upon responding was slightly different between marmosets. After preliminary training the level of noncontingent reward delivery thus had to be titrated individually for each marmoset. Two subjects were found to react optimally to $P\left(O \mid\sim A\right) = 0.02$ and two to $P\left(O \mid\sim A\right) = 0.03$.

A major difference between the current paradigm and that of Jackson et al. 2016 is use of a single stimulus, rather than linking a distinct stimulus to each of the action–outcome pairings. As the marmosets cannot use the stimulus to distinguish between the outcomes, they must be using action–outcome associations to perform the task, and the degradation of the contingency of those action–outcome associations must drive the effect of noncontingent reward on behaviour. The rationale for the design and subsequent interpretation is similar to that used in a recent outcome devaluation study, in which rhesus monkeys performed two distinct actions, targeted at identical stimuli, to receive two outcomes, only one of which was devalued (Rhodes and Murray 2013). However, a limitation of both investigations is that neither have been able to entirely eradicate potential stimulus–outcome associations from the task, as it is plausible that stimulus–based spatial location–outcome associations could could contribute to the control of behaviour.

One of the functions most consistently ascribed to the OFC is its role in encoding the value of outcomes and the formation of outcome expectancies. At first glance, faulty valuation of reward could explain the present finding of lessened impact of noncontingent reward following OFC inactivation – if OFC dysfunction led to the formation of altered outcome expectancies in which reward were undervalued, one would predict increased reward seeking and thus a higher response rate. However, OFC inactivation was shown to have no impact upon responding in baseline sessions in the control experiments, suggesting that the explanation is not so simplistic.

Thus, neither outcome expectancies, nor any of the other theories of OFC function that are currently in vogue, appear sufficient to explain the current dataset. And nor can the mediation of sensitivity to noncontingent reward be extrapolated to explain the wealth of other experimental findings that concern the OFC. The search for a universal theory of OFC function, whilst appealing, is almost certainly futile. The OFC must have multiple functions, and these functions are utilised in different ways depending on the environmental context. Conversely, it seems highly unlikely that any function will be solely mediated by the OFC alone, and that instead responsibility for the control of a given psychological process would be shared by multiple brain regions, in accordance with the adaptive principle of redundancy.

The present findings provide insight into the precise role played by the OFC in contingency learning. One could consider the following equation which describes the concept of contingency, where $P(O|A)$is the probability of receiving the outcome given the action, and $P(O| \sim A)$ is the probability of receiving the outcome in the absence of the action

$$contingency = P(O|A) - P(O| \sim A)$$

Computationally, both probabilities would need to be known and tracked in order to calculate contingency, which would entail the monitoring of how frequently reward was received after performing the action, how frequently reward was received in the absence of the action, and the use of a comparator to subtract one observation from the other. Reduced sensitivity to noncontingent reward following OFC inactivation suggests that the OFC may contribute to the knowledge of contingent relationships via the monitoring of $P(O| \sim A)$, but, given the intact differential responding in the degraded and nondegraded sessions, that the area is not needed in order to compute contingency from the relevant probabilities.

On the contrary, the finding that upon inactivation of the pgACC, differential responding in the nondegraded and degraded sessions is lost suggests that it is the pgACC which is critical for the actual calculation or use of contingency estimates. The results appear to replicate the classic contingency degradation deficits which have been found previously in rodents and are thus in agreement with the rodent literature surrounding the role of the PL in sensitivity to contingency degradation and in the goal-directed actions more generally, providing further support for pgACC (area 32) of the primate as a functional homologue of rodent PL, an assertion made in Jackson et al. 2016 and corroborated by similarities in cytoarchitecture and receptor distribution (Gabbott et al. 2003; Vogt et al. 2013). Excitotoxic lesions or DA depletion of the PL reduce sensitivity to contingency degradation (Balleine and Dickinson 1998a; Naneix et al. 2009 but see Lex and Hauber 2010), while selective knockdown of *brain-derived neurotrophic factor* in the region was found to increase contingency degradation sensitivity (Hinton et al. 2014). Response to outcome revaluation was similarly impaired by PL excitotoxic lesions (Corbit and Balleine 2003; Killcross and Coutureau 2003; Coutureau et al. 2009) and exposure to chronic stress, which is known to induce atrophy of the mPFC including the PL (Radley et al. 2004; Cerqueira et al. 2007a), causes impairments in both paradigms (Dias-Ferreira et al. 2009). Intriguingly, large lesions of the mPFC that included both the PL and IL replicated the deficit in sensitivity to contingency degradation, but showed that lesions of the PL do not affect normal responding in another test of changing action-outcome contingency: an omission test[1] (Coutureau et al. 2012).

In electrophysiological work, activity relating to specific action-outcome associations was found in the rat PL, though the neuronal sampling also included cells in the anterior cingulate cortex (Mulder et al. 2003 but see Kargo et al. 2007 where action-outcome association-related activity in mice was identified in another region of the mPFC known as the second frontal (Fr2) or medial precentral area (Van De Werd et al. 2010)). Furthermore, PL lesions resolve conflict between action-outcome and stimulus-response representations in the control of behavioral output by reducing the influence of the former (Dwyer et al. 2010). Findings which do not entirely fit with the present data are two studies in which it was shown that PL lesions or inactivation that occurred post- as opposed to pre-training had no impact upon sensitivity to outcome devaluation, thus suggesting that the PL was involved in the acquisition but not expression of outcome-associations (Ostlund and Balleine 2005; Tran-Tu-Yen et al. 2009). In the current paradigm, subjects are very well trained before undergoing pgACC inactivation during contingency degradation, and thus it would appear that in the marmoset the role of the pgACC with respect to action-outcome associations cannot be limited to their acquisition, as that of the PL appears to be in the rat.

[1] In reward omission an animal is trained to associate a reward with an action before the action-outcome contigency is changed completely and withholding the action instead becomes linked to reward (Dickinson et al. 1998).

The finding of the present investigation that OFC inactivation reduces the sensitivity of marmosets to noncontingent reward delivery can also be considered in the context of the contribution of the OFC to extinction learning. Extinction usually entails the complete omission of the outcome, whilst contingency degradation, as used in the present study, similarly involves the breaking of the link between action and outcome but with continued outcome delivery, thus obviating emotional effects of frustrative non-reward (Amsel 1958; 1962; 1992) that occur following complete reward omission. Contingency degradation can thus be considered to be an analogous process to extinction and is thought to depend upon the same associative changes (Rescorla 2001) while allowing a more accurate assessment of the effects of interrupting the action-outcome association (Rescorla and Skucy 1969).

The OFC has been linked to extinction using a range of experimental techniques and paradigms. PET and fMRI studies in humans demonstrate OFC activation during extinction (Hugdahl et al. 1995; Gottfried and Dolan 2004) and the ablation of macaque OFC have been shown to impair instrumental extinction (Butter et al. 1963; Butter 1969; Izquierdo and Murray 2005). Moreover, excitotoxic lesions of the OFC in marmosets induce an impairment in a Pavlovian one-trial extinction paradigm; marmosets showed prolonged cardiovascular arousal upon premature termination of a conditioned stimulus and reward omission (Reekie et al. 2008). Recently, more selective excitotoxic lesions within the OFC of macaques, specifically the more medial area 14 but not the lateral region of area 11/13, produced impairments in extinction, which doubly dissociated with the effects of area 11/13 (but not area 14) lesions on reinforcer devaluation (Rudebeck and Murray 2011), a result which fit with the finding that the thickness of medial OFC correlated with stronger extinction memory during recall in humans (Milad et al. 2005). In contrast, it was the inactivation of lateral OFC that was demonstrated to impair extinction recall in rodents (Panayi and Killcross 2014). The present deficit in sensitivity to the delivery of noncontingent reward occurring after intra-OFC muscimol administration implicates more lateral parts of the OFC, the region targeted by the cannulae, which would agree with the data of Panayi and Killcross 2014 and could suggest that the extinction deficits associated with area 14 (Rudebeck and Murray 2011) may not necessarily be related to insensitivity to contingency per se, but may instead be due to effects on the emotional sequelae of extinction.

In summary, it has been demonstrated that the OFC and pgACC are both necessary for normal contingency learning, but do not mediate the same psychological processes. Inactivation of the pgACC induces a classic insensitivity to contingency degradation deficit whereby differential responding in the degraded and nondegraded conditions is eradicated. In contrast, inactivation of the OFC more generally reduces behavioural sensitivity to contingency degradation across all conditions, but leaves differential responding in the degraded and nondegraded conditions intact. A novel contingency degradation task, suited to the implementation of multiple acute manipulations, was developed specifically for this study. In future work the contribution of the OFC and pgACC could be further specified by investigating the impact of particular neurotransmitters and receptor subtypes, and results should be extended by exploring the contribution of neighbouring areas of PFC to sensitivity to contingency degradation, including area 14/10 which is implicated in human neuroimaging studies (Tanaka et al. 2008; Liljeholm et al. 2011).

6 General Discussion

6.1 Summary of results

The experiments in this thesis were designed to investigate different aspects of neuropsychopharmacology implicated in OCD, a debilitating neuropsychiatric disorder associated with dysfunction in the limbic cortico-striato-thalamo-cortical (CSTC) circuitry including the OFC, caudate, and amygdala, and with the neurotransmitters serotonin (5-HT) and dopamine (DA). OCD is the archetypal disorder of compulsivity, a neurocognitive trait which can be deconstructed and evaluated either in terms of cognitive inflexibility or as an imbalance between the habitual and goal-directed action systems in the control of behaviour. Two behavioural paradigms have therefore been used in the thesis, reversal learning and contingency degradation, each of which is regarded as a prototypical test of either cognitive flexibility or goal-directed actions and habits respectively.

In chapter 3, the underpinnings of the well-validated OFC 5-HT depletion-induced reversal learning deficit (Clarke et al. 2004; 2005; 2007) were investigated. First, the downstream neurochemical effects of OFC 5-HT depletion were explored by HPLC-ED analysis of 5-HT and dopamine levels in subcortical regions following 5,7-DHT lesions of the OFC. The lesions were made unilaterally, to allow the comparison of regions in the OFC 5-HT-depleted hemisphere to be compared to those in the nondepleted hemisphere, thus using each animal as its own control. Given the strong anatomical links with the OFC, and their implication in OCD neuroimaging and evidence of involvement in reversal learning, a range of regions of the striatum as well as the amygdala were analysed. There were no consistent neurochemical changes in any part of the striatum but a robust increase in dopamine levels was found in the amygdala.

The striatum was the focus of chapter 4, utilising the serial reversal learning paradigm (Rygula et al. 2010), which had been specifically designed to accommodate acute, repeated manipulations and incorporated two phases, a retention and a reversal phase. It is currently unclear precisely which regions of the striatum contribute to reversal learning, as both the ventromedial caudate (vm caudate) and the putamen have recently been implicated in performance of the task in non-human primates (Clarke et al. 2011; Groman et al. 2013). To clarify the roles of both regions in the context of reversal learning marmosets were trained on the serial reversal learning paradigm and then surgically implanted with indwelling cannulae targeting the vm caudate and the putamen. After extensive training to establish stable baseline performance on the task, the regions were inactivated via the infusion of muscimol, a $GABA_A$ agonist on probe sessions. Intra-putamen muscimol induced a dose-dependent impairment on the task selective to the reversal phase, while preliminary intra-caudate muscimol data were suggestive of a generalised impairment that affected both phases of the task. The marmosets were highly overtrained on the task, and thus it was argued that

the deficit might result from impairments in the habitual control of behaviour, in which the putamen has been identified as a critical locus (Miyachi et al. 1997; 2002; Fernandez-Ruiz et al. 2001; Deffains et al. 2010; Redgrave et al. 2010 but see Desmurget and Turner 2010).

Habitual, as opposed to goal-directed, control of behaviour then also formed the focus of chapter 5. In a study recently published by my laboratory it was shown that with lesions of the OFC or perigenual anterior cingulate cortex (pgACC) the responding of marmosets became insensitive to contingency degradation, thus manifesting as being under habitual, and not goal-directed, control (Jackson et al. 2016). The experiments of chapter 5 aimed to further clarify the contributions of the OFC and pgACC to sensitivity to contingency degradation; marmosets were trained on a novel version of the contingency degradation paradigm suited to the application of acute manipulations and surgically implanted with indwelling cannulae targeting both regions. Intra-OFC inactivation via the infusion of a combination of muscimol and baclofen ($GABA_A$ and $GABA_B$ agonists respectively) caused a general reduction in the sensitivity of marmosets to the delivery of noncontingent reward, while pgACC inactivation selectively impaired their sensitivity to the alteration of specific action-outcome contingencies.

6.2 Methodological considerations

6.2.1 The common marmoset as a model for the neuropsychopharmacology of OCD

All the studies that formed part of this thesis were conducted using the common marmoset (Callithrix jacchus) as a model species. Marmosets, like other non-human primates, have a prefrontal cortex (PFC) the structure and functional organization of which bears great resemblance to that of human PFC, especially in comparison to the relatively less developed PFC of the rodent, which is markedly less similar to human PFC and displays different patterns of hodology (Uylings and Eden 1991; Brown and Bowman 2002). The primate frontal cortex is hyperscaled relative to the rest of the brain (Bush and Allman 2004), and primates are also cytoarchitectonically unique in their possession of a small-celled granular layer in the PFC which is not found in other mammals, including rats (Uylings et al. 2003; Teffer and Semendeferi 2012). The striatum too has greater similarity to humans compared with that of rodents, the most obvious characteristic of which is that in primates the striatum is subdivided into the caudate and putamen by the white matter tracts of the internal capsule, while rodent striatum exists as a single undivided structure (Albin et al. 1989; DeLong 2000).

It has been argued that the greater homology between non-human primate frontal cortex and that of a human makes such species particularly valuable as translational models of aspects of human neuropsychiatric disease, which is often associated with abnormalities in the PFC (Roberts 1996; Oikonomidis et al. 2016). Furthermore, behavioural tasks in the non-human primate usually exclusively utilise visual and/or auditory stimuli, due to the fact that in non-human primates, as in humans, vision and audition are the dominant senses, in contrast to the much greater reliance on olfaction in rodents (Oikonomidis et al. 2016); similarities in sensory dependence between non-human primates and humans are paralleled by the high degree of functional and anatomical correspondence found in sensory and associative brain

regions between the species (Orban et al. 2004; Fattori et al. 2009; Rauschecker and Scott 2009; Mantini et al. 2012; Orban 2016).

The common marmoset is increasingly popular in neuroscience as a model non-human primate species (Abbott et al. 2003; Hart et al. 2012; Burkart and Finkenwirth 2015), and as such there has been a concomitant rise in interest in the attempt to understand the anatomy of the marmoset brain, with many detailed papers and atlases devoted to the subject having been published (Krubitzer and Kaas 1990; Burman et al. 2006; 2008; 2011, a; b; 2014; 2015; Roberts et al. 2007; Palazzi and Bordier 2008; Burman and Rosa 2009; Reser et al. 2009; Yuasa et al. 2010; Hardman and Ashwell 2012; Paxinos et al. 2012; Mothe et al. 2012). Furthermore, marmosets, as with all New World monkeys, are known to be much more sexually monomorphic in their general anatomy than apes or Old World monkeys (Snowdon 1998), and there is evidence to suggest that they have a very low level of sexually dimorphic gene expression in the brain (Reinius et al. 2008). The natural implication, that there are relatively few neural sex differences in marmosets, aids the interpretation of the experiments described within this thesis, as due to constraints in marmosets available to be allocated to studies (§B.5), all studies had an unbalanced male:female subject ratio.

Relatedly, there has also been a surge in efforts to chronicle the behavioural repertoire of marmosets (Stevenson and Poole 1976; Pistorio et al. 2006; Bezerra and Souto 2008; Buchanan-Smith and JB Carroll 2010), and of particular relevance to the work in chapter 4, several studies have recently been published that detail the normal performance of common marmosets on reversal learning paradigms (Takemoto et al. 2015; Kangas et al. 2016). There are also many practical advantages to using marmosets as research subjects. Marmosets, due to their small size, can be easily kept in spacious conditions within a laboratory (Mansfield 2003; Okano et al. 2012; Kishi et al. 2014), and the creation of a stimulating, environmentally-enriched environment is more readily attainable for marmosets compared to species such as rhesus macaques with more complex needs (Smith et al. 2001; Mansfield 2003). Marmosets are also reproductively efficient and relatively easily bred within laboratories, and a combination of short gestation periods and how quickly they reach sexual maturity enables breeding to be scaled up and down to meet laboratory demands (Abbott and Hearn 1978; Mansfield 2003; Zühlke and Weinbauer 2003; Okano et al. 2012; Kishi et al. 2014).

The behavioural tasks in this thesis were all conducted using an automated touchscreen apparatus, with visual stimulus presentation upon the touchscreen, auditory stimulus playback and milkshake/juice reward delivery controlled by modules within the MonkeyCantab program (R.N. Cardinal) using the Whisker control system (Cardinal and Aitken 2010). Much has been written about the advantages of the use of automated testing apparatuses over manual experimenter-controlled task implementation, but discussion has normally focussed on the use and refinement of such apparatuses with rodents (Bussey et al. 1994; 2001; 2008; 2012; Morton et al. 2006; Talpos et al. 2012; Horner et al. 2013; Mar et al. 2013; Nithianantharajah et al. 2015; Kumar et al. 2015; Brady and Floresco 2015), despite widespread uptake of the technology by non-human primate researchers from my laboratory and from other groups, working with squirrel monkeys (Kangas and Bergman 2012; 2014; 2016), rhesus monkeys (Weed et al. 1999; 2008; Buckley et al. 2001; 2004; 2008; Taffe et al. 2002; Taffe 2004; 2012, a; b; Wilson et al. 2007; 2010; Kwok and Buckley 2009; Ginsburg et al. 2014) and marmosets (Pearce et al. 1998; Crofts et al. 1999; Pryce

et al. 2004; Spinelli et al. 2004; 2005; 2006; Hauser et al. 2008; Takemoto et al. 2011; Rygula et al. 2014). Consequently, while some advantages that are often asserted with respect to rodents, for example the simultaneous testing of multiple animals leading to faster subject throughput, are not applicable in this case (marmosets were tested singly so that performance could be closely monitored by video camera), many reasons for the use of automated apparatuses are equally pertinent to rodent and marmoset testing. Such apparatuses not only improve the ease and accuracy of task administration and data collection (Bussey et al. 2008; 2012; Horner et al. 2013), but also help lessen the influence of any unintended experimenter bias (Bussey et al. 2001), and mediate better translation of findings in animals to humans via improved construct validity (Bussey et al. 2001; Morton et al. 2006; Talpos et al. 2012; Mar et al. 2013; Horner et al. 2013; Nithianantharajah et al. 2015).

The translation of findings into a greater understanding of particular cognitive processes, and their dysfunction, in humans, was one of the main motivations behind the experiments that formed part of this thesis. The experiments were chosen to expand the current knowledge of the neurobiological underpinnings of two psychological processes, reversal learning and contingency degradation, each of which act as a window into a major psychological conceptualization of compulsivity and therefore of OCD. Translational neuroscience is heralded as an important tool to aid the advancement of our understanding of such complex, multi-faceted disorders, with the hope that by modelling in animals aspects of cognition relevant to an illness, be it neurological or neuropsychiatric, we can gain information that may ultimately lead to new drug targets and discoveries (Markou et al. 2009; Keeler and Robbins 2011; Day et al. 2011; Schoepp 2011; Robbins 2012; Talpos and Steckler 2013; Homberg 2013; Wallace et al. 2015).

6.2.2 The use of repeated, acute manipulations to perturb neural activity

Each investigation in the thesis utilised acute drug infusions as a core experimental technique. The infusions, which necessitated stereotaxic surgery to implant indwelling cerebral cannulae targeting the respective regions (§2.4.3.2), then permitted the repeated, acute manipulation of those regions without difficulty, and with minimal restraint and distress for the marmosets. Not only did the use of acute drug infusions also reduce the number of marmosets that needed to be used in the experiments, compared to the number that would have been used in lesion-based designs, as already described (§4.4 and 5.4), they gave numerous, important scientific benefits as well. It has been made clear in previous work that, with careful experimental design, infusions can provide great utility, as the activity in specific areas can be reversibly perturbed at times restricted to specific phases of a task (e.g. Herry et al. 2008; Clarke et al. 2015). In the present work, their use in the investigations of chapters 4 and 5, allowed the comparison of behaviour in probe inactivation sessions to baseline responding. Comparing to a local baseline level of performance reduced the impact of variation in responding both between subjects and within the same subject over time, making it easier to see the effect of the manipulations. At the neural level, infusions also eliminated the possibility of compensatory contributions from other brain regions masking the true effect of a manipulation, which can be problematic with lesion-based studies, particularly given the time that must be given for an animal to recover after surgery before testing can be resumed (Dias and Segraves 1996).

It is thus clear that drug infusions are a valuable addition to the arsenal of techniques available to investigate learning and cognition in behavioural neuroscience, a challenging field in which investigators attempt to resolve behaviours and their underlying psychological basis, with no simple assay to distill the complicated situation into easy answers (Cahill et al. 2001). That is not to say that there are no problems with the technique. The precise position of the cannulae cannot be known until after the animal is euthanased and histology is consulted, and additionally there is no definitive evidence of the spread of a drug, as is apparent in the histology of lesioned subjects; instead researchers make calculated estimates based on previous data and adjust the volume and infusion rate of a drug accordingly (Gallo 2007). However, the technology was key to the execution of the experiments in this thesis, and will likely continue to be used in future work concerning reversal learning and contingency degradation, the neural and psychological interpretations of which is not straightforward, as discussed in the next section.

6.3 A synthesis of the results in this thesis

The findings in this thesis are all broadly inter-related – each investigates the neural underpinnings of a behavioural paradigm, reversal learning or contingency degradation, in which marmosets must adapt their responding to changing action-outcome contingencies. Furthermore, both reversal learning and contingency degradation assess abilities/constructs, in cognitive flexibility and the balance between goal-directed actions and habits respectively, which are thought to characterise compulsivity and which have been demonstrated to be associated with OCD in studies with patients. However, each study has used its own paradigm, and has investigated the neural basis of that paradigm in different brain regions. The results of each chapter therefore elucidate different facets of cognitive flexibility and the balance between goal-directed actions and habits, and therefore different aspects of compulsivity, and hence take their place in their own distinct yet closely related literatures of previous research.

Results from chapters 3 and 4 both concerned reversal learning and cognitive flexibility. Reversal learning is a paradigm in which animals experience the reversal of a set of stimulus/action-outcome contingencies and must change their behaviour accordingly. The paradigm begins with the need for subjects to learn to discriminate between two stimuli and to bias responding to that which is linked with reward. That the psychological processes involved in this preliminary stage remain intact and are not the cause of any impairments seen later on in testing is controlled for in both paradigms used in the thesis. In chapter 3 marmosets are allowed to recover following surgery and then are tested on the retention of a discrimination learnt prior to surgery, whereas in chapter 4 each daily testing session begins with a retention phase in which stimulus/action-outcome associations are the same as at the end of the previous day.

Once subjects have learnt to respond to a certain criterion of performance on a discriminative set, they are exposed to a reversal of contingencies and their ability to reverse their responding assessed. Successful performance requires several interconnected processes to be intact. Subjects must first be able to detect the changed contingencies; they must be able to register that the reward expected from their responding is no longer being delivered, presumably through the use of a prediction error. In both paradigms used, this process is relatively easy compared to what could be required in alternative task designs as the paradigms are deterministic not probabilistic, and thus subjects can gain complete information about the currently

relevant contingencies from one trial and do not have to make assessments across trials. Secondly, subjects must stop responding to the previously rewarded stimulus, they must inhibit the prepotent urge to respond as they had been doing. Thirdly, they must respond to the other available stimulus, a process which requires subjects to overcome their learned avoidance of the stimulus/action. Finally, they must form new stimulus/action-outcome associations regarding the stimulus to replace their old ones, forming a fresh outcome expectancy. In the serial reversal paradigm of chapter 4, an additional process is at work: subjects learn rules to help them solve each reversal, which are presumably akin to task or attention switching given negative feedback, as evidenced by the literature on learning set formation and the progressive improvements seen in reversal performance over time, and demonstrated in marmosets performing this task previously (Rygula et al. 2010).

The OFC 5-HT depletion-induced reversal learning deficit which is the focus of chapter 3 has been theorised to be dependent upon a specific impairment in the ability to inhibit the prepotent urge to respond to the previously correct stimulus, an interpretation suggested from the first by the perseverative nature of the impairment (Clarke et al. 2004; 2005) and conclusively demonstrated in a test specifically designed to separate out the possible psychological substrates of the deficit (Clarke et al. 2007). An inability to inhibit prepotent responding could be thought of as compulsive behaviour, but is also highly reminiscent of impulsivity, a trait in which subjects act prematurely and inappropriately (Durana and Barnes 1993; Dalley et al. 2011). Inhibitory control is at the core of many tasks designed to assess impulsivity including the go/no-go, detour reaching, stop signal reaction time, 5-choice serial reaction time and delay discounting tasks. Moreover, there are several instances in which impulsivity has been linked to the OFC: humans with damage to the OFC exhibit impulsive behaviour (Rogers et al. 1999b; Bechara et al. 2000) while lesions of the region in animal studies impair performance in a detour reaching task (Wallis et al. 2001), in the stop-signal reaction time task (Eagle et al. 2008), and in the 5-choice serial reaction time task (Chudasama et al. 2003). OFC lesions or inactivations give mixed results in delay discounting, with reports of increased impulsivity (Mobini et al. 2002; Rudebeck et al. 2006), decreased impulsivity (Winstanley et al. 2004) or no effect (Jo et al. 2013; Stopper et al. 2014), differences which may be due to dissociable effects of different subregions of the OFC (Mar et al. 2011) or levels of baseline impulsivity (Zeeb et al. 2010). There is also evidence that DA within the OFC may be more important than 5-HT for this task (Kheramin et al. 2004; Winstanley et al. 2006; 2010). Levels of the transcription factor ΔFosB (Nestler et al. 2001) in the OFC were associated with cocaine withdrawal-induced impulsive responding (Winstanley et al. 2009) and altered recruitment of the OFC has been demonstrated in drug addicts (Volkow and Fowler 2000), addiction being the archetypal disorder of impulsivity (Jentsch and Taylor 1999; Bechara 2005).

Impulsivity is also relevant to the discussion of compulsivity and OCD. Impulsivity has long been theorised to interact with OCD (Lopez-Ibor 1990; Torregrossa et al. 2008), with OCD patients scoring more highly than controls on scales of impulsivity (Richter et al. 1996; Summerfeldt et al. 2004; Boisseau et al. 2012; Benatti et al. 2014 but see Stein et al. 1994), and exhibiting deficits in the stop signal reaction time task (Chamberlain et al. 2006a; McLaughlin et al. 2016). Impulse-control disorders are frequently comorbid with OCD (e.g. ADHD - see §1.2.3.3; Grant et al. 2006a), and high impulsivity in OCD is associated with greater symptom severity and poorer prognosis (Kashyap et al. 2012b).

The preliminary behavioural data in chapter 3 suggest that the OFC 5-HT depletion-induced reversal

learning deficit may be mediated via the downstream upregulation of amygdala dopamine. That the OFC and the amygdala interact is agreed upon by the multiple groups working to investigate their joint involvement in reversal learning, but there are several different theories of the nature of the relationship between the two regions: Schoenbaum and colleagues advocate that the OFC encodes prior action-outcome associations which drive the flexible encoding of new associations in the amygdala via error signals (Schoenbaum et al. 2009), Morrison and Salzman and colleagues that the relative contribution of the OFC and the amygdala is valence dependent (Morrison et al. 2011), and Rushworth and colleagues that the interaction of the regions acts to emphasise relevant rewards relative to irrelevant rewards in the process of credit assignment (Chau et al. 2015). The findings in chapter 3 could be argued to suggest a fourth possibility, based upon the prior work of Clarke et al. 2007, that OFC serotonin, via the upregulation of amygdala DA, is involved in the inhibition of prepotent responses to previously rewarded stimuli.

Whilst the work described in chapter 3 attempted to elucidate the contributions of the OFC and amygdala, the study in chapter 4 focused on the role of the striatum in reversal learning. Between them, chapters 3 and 4 cover the three main regions that have been identified as the main reversal learning loci. However, the paradigms used have important differences in their design: in chapter 3 reversal learning is tested in acquisition, and subjects have no prior experience of reversals, while in chapter 4, in the serial reversal learning paradigm, subjects undergo extensive training to achieve a stable level of reversal performance, which is then perturbed using acute inactivations of the striatal areas.

The serial reversal learning paradigm had previously been validated in the laboratory in Rygula et al. 2010. Performance of marmosets over the course of the task was characterised for the first time, and the OFC lesion-induced reversal learning deficit previously shown in the laboratory with the acquisition reversal learning task (Dias et al. 1996a) was replicated in the new paradigm. As well as the OFC, Rygula et al. 2010 also demonstrated that lesions of the vlPFC impaired reversal learning performance on the paradigm, an effect ascribed to a role for the vlPFC in the application of rules that form the reversal learning set to new contexts: vlPFC-lesioned marmosets could perform normally when given stimuli with which they were familiar pre-surgery, but displayed impaired reversal learning with fresh stimuli supplied post-surgery. The nature of the finding in chapter 4, that inactivation of the putamen impaired serial reversal learning, is difficult to compare to those deficits seen in Rygula et al. 2010 due to the use of acute manipulations instead of lesions, though it superficially appears more similar to the OFC lesion deficit, as subjects in chapter 4 displayed impairments despite using the same set of stimuli throughout the experiment. When the full histological dataset for the study is available it will be possible to compare the location of the putamen cannulation site to the map of PFC projections into the striatum described in Roberts et al. 2007, though the target region of the putamen appears, according to Roberts et al. 2007, to receive projections from the medial, orbital and lateral PFC. Further experiments could attempt to replicate the OFC and vlPFC lesion deficits in the task using acute inactivations to facilitate direct comparison of the deficits.

The task was ideally suited to the experimental aims of chapter 4: to compare the contributions of the vm caudate and putamen to reversal learning, following the implication of each in the task by the studies of Clarke et al. 2011 and Groman et al. 2013 respectively. The involvement of both brain regions was compared within-subject and findings suggest that it was the putamen that played a reversal-specific role, with inactivation of the vm caudate having a more general effect. The results could be interpreted in two

different ways. The first possibility is that the results support the findings of Groman et al. 2013 and appear to conflict with those of Clarke et al. 2011: the putamen and not the vm caudate are necessary for normal reversal learning. The second possibility is that, due to substantial overtraining, task performance became habitual, and inactivation of the putamen impaired this habitual control. Further characterisation of the putamen inactivation-induced deficit, perhaps via its direct comparison with deficits induced by vlPFC or OFC inactivation, is necessary to clarify its psychological basis.

Finally, in chapter 5, the pgACC and OFC were shown to play a differential role in mediating behavioural sensitivity to contingency degradation. A plethora of studies have linked the prelimbic cortex (PL) to goal-directed behaviour (Balleine and Dickinson 1998a; Corbit and Balleine 2003; Killcross and Coutureau 2003; Coutureau and Killcross 2003; Naneix et al. 2009; Hinton et al. 2014), but determination of the homologous region to the PL in the non-human primate is not straightforward (Jackson et al. 2016). With respect to the OFC, the homology between non-human primates and rodents is clearer, and in addition to rodent work, there have also been studies in rhesus monkeys and humans linking the OFC to goal-directed behaviour directly. However, different studies have pinpointed the locus of interest to be either more medial regions of the OFC (Gottfried et al. 2003; Valentin et al. 2007; Gourley et al. 2010) or more lateral regions (Rudebeck and Murray 2011; Gremel and Costa 2013), and there is debate as to whether the OFC supports the encoding of stimulus-outcome (Ostlund and Balleine 2007) or action-outcome associations (Rhodes and Murray 2013).

A recent study from my laboratory confirmed that lesions of either the OFC or pgACC were shown to impair sensitivity to contingency degradation (Jackson et al. 2016). Nonetheless, the result in Jackson et al. 2016 could not elucidate which specific psychological processes were made dysfunctional by each of the lesions and thus could not assess the psychological underpinnings of the deficits. Jackson et al. 2016 could thus not confirm whether the nature of the deficits was the same for the two regions, or alternatively if their involvement relied upon distinct contributions to behaviour.

The new paradigm used in chapter 5 allowed a more finely-grained analysis of behaviour than was possible previously, and the results of the experiment did dissociate the differential contributions of the OFC and the pgACC to sensitivity to contingency degradation. The OFC was found to mediate general sensitivity to noncontingent reward; the suppressive effect of noncontingent reward delivery was lessened in both the degraded and nondegraded sessions following OFC inactivation. Such insensitivity to noncontingent reward would impair an animal's ability to make accurate judgements of the strength of action-outcome associations and could therefore lead to inappropriate over-responding. In short, an insensitivity to non-contingent reward could be theorised to account for persistent habit-like behaviour. The marmosets in the study have not yet been euthanased at the time of writing, so histological analysis of the cannulae placement has not yet been performed. However, the more lateral portion of the OFC was the area targeted, and if the cannulae placement is found to be accurate the results will support those previous findings which have linked lateral OFC to goal-directed actions (e.g. Rudebeck and Murray 2011). Additionally, the paradigm was designed to minimise the use of stimulus-outcome associations in task performance, and thus the result supports work such as Rhodes and Murray 2013 that highlights a role of the OFC mediating the encoding of action-outcome associations. In a broader context, the result is in accord with

recent functional neuroimaging work where the excessive habit formation seen in OCD was linked to hyperactivation (Gillan et al. 2014a) and reduced grey matter volumes (Voon et al. 2014) in the OFC.

The deficit seen as a result of inactivation of the pgACC, in contrast to that induced by inactivation of the OFC, was reflective of a selective impairment in sensitivity to the degradation of specific action-outcome contingencies; differential suppression of responding between the degraded and nondegraded sessions was ceased. The deficit is of the same form as that originally reported following lesions of the rat PL (Balleine and Dickinson 1998a), and subsequently reported as a result of several other types of PL perturbations (Naneix et al. 2009; Hinton et al. 2014), further strengthening the assertion made in Jackson et al. 2016 that the pgACC is functionally homologous to the rat PL. However, in a similar study recently conducted with rhesus monkeys, Rhodes and Murray 2013 investigated whether lesions of the pgACC (area 32, called PL in their study) disrupted sensitivity to outcome devaluation, as per the rodent literature, and observed equivocal results. That the lesions in Rhodes and Murray 2013 only extended across 55-83% of the intended area could potentially account for the equivocal results seen in their study, or the disparity between the present findings and those in Rhodes and Murray 2013 could instead be due to species or task differences between outcome devalutation and contingency degradation.

The findings regarding the pgACC can be considered in the context of evidence that implicates the region in the pathology of OCD. The ACC is the site of a much-researched neurocognitive deficit in OCD, augmented error-related negativity (ERN; Gillan et al. 2016a). The ERN, the origin of which has been localised to the ACC (Debener et al. 2005), has been shown to be enhanced in a plethora of studies of OCD patients (Gehring et al. 2000; Johannes et al. 2001; Ruchsow et al. 2005; 2007; Hajcak et al. 2008; Endrass et al. 2008; 2010; 2014; Endrass and Ullsperger 2014; Stern et al. 2010; Xiao et al. 2011; Riesel et al. 2011; 2015; Hanna et al. 2012; Carrasco et al. 2013a; b; Grützmann et al. 2014; Klawohn et al. 2014; Liu et al. 2014 but see Nieuwenhuis et al. 2005; Agam et al. 2014; Weinberg et al. 2015; Mathews et al. 2016) and in individuals with subclinical obsessive-compulsive symptoms (Hajcak and Simons 2002; Kaczkurkin 2013; Zambrano-Vazquez and Allen 2014), and has been theorised to be related to anxiety (Gillan et al. 2016a). Furthermore, in an event-related fMRI study, OCD patients were observed to show increased recruitment of the dACC during error commission in an interference task, with the precise localisation of the differential activity relative to control subjects in the rostral part of the pgACC (Fitzgerald et al. 2005). The ACC is a region frequently identified to be hyperactive in resting state neuroimaging studies of OCD (Table A.1; McGovern and Sheth 2016) and has been incorporated in models of the dysfunctional CSTC circuitry thought to underlie the pathology of the disorder (Menzies et al. 2008; Maia et al. 2008). Finally, several forms of treatment centred on the ACC have proved efficacious in OCD including anterior cingulotomy (Jenike et al. 1991; Baer et al. 1995; Dougherty et al. 2002; Kim et al. 2003a; Jung et al. 2006; Brown et al. 2016) and most recently deep Transcranial Magnetic Stimulation of the region (dTMS; Carmi et al. 2015; Zangen et al. 2016; Grant et al. 2016)

The pgACC data also fit with the wider literature concerning stress, the controllability of outcomes and contingency. Stress has long been linked to dendritic remodelling in the mPFC in rodent studies (Wellman 2001; Seib and Wellman 2003; Cook and Wellman 2004; Radley et al. 2004; Radley and Morrison 2005; Radley et al. 2005; 2006; 2008; Brown et al. 2005; Liston et al. 2006; Izquierdo et al. 2006a; Cerqueira et al. 2007b; a), and this has been further linked to deficits in contingency degradation and outcome

devaluation (Dias-Ferreira et al. 2009). Other work has shown that the controllability of stress is a factor in its deleterious effects; inactivation of the ventral mPFC (covering both PL and IL) in rats prevents its inhibition of the dorsal raphe nucleus in the face of controllable as opposed to uncontrollable stress, thus removing the block upon behavioural sequelae of stress (Amat et al. 2005).

The factor of controllability is of key relevance for the understanding of depression. Humans and animals that are repeatedly exposed to uncontrollable aversive outcomes become less likely to attempt to avoid those outcomes in the future (Overmier and Seligman 1967; Seligman and Maier 1967; Hiroto 1974; Hiroto and Seligman 1975) in a phenomenon known as learned helplessness (LoLordo 2001). Uncontrollability describes a zero contingency condition between a subject's actions and the outcome (Seligman et al. 1971) and is thought in certain circumstances to induce an impairment in a subject's ability to perceive contingent relationships between their subsequent behaviour and events (Maier and Seligman 1976; Abramson et al. 1978). Experimental work in rodents has linked learned helplessness to stress and the mPFC: in mice uncontrollable stress has been shown to modify synapses on mPFC neurons, and the enhancement of activity of the same neurons to convert resilient behaviour into learned helplessness (Wang et al. 2014). Learned helplessness has been proposed to account for the symptomatology of depression (Seligman 1975; Rosenhan and Seligman 1984); it has been shown that control subjects exposed to laboratory-induced learned helplessness show similar deficits to depressed patients on a test of problem solving (Miller and Seligman 1975). Altered perception of contingency may also be relevant for OCD; OCD patients give estimates of action-outcome contingencies that are at variance with those given by control subjects (Reuven-Magril et al. 2008; Gillan et al. 2014b) and have recently been found to exhibit a dissociation between their subjective estimate of contingency and their behaviour in an instrumental contingency task (Matilde Vaghi, personal communication). Conceptually similar to that of learned helplessness is the theory of orientation of locus of control: subjects have an internal locus of control if they tend to believe outcomes to be contingent on their own actions and an external locus if they believe outcomes are independent of their actions (Rotter 1966; Rotter 1975). Subjects with greater externality fail to show a measured response to success and failure (Lefcourt 1972) and show increased levels of learned helplessness (Hiroto 1974) and depression (Benassi et al. 1988; Mirowsky and Ross 1990; Grote et al. 2007; Zampieri and Pedroso de Souza 2011 but see Abramson et al. 1978).

6.4 Psychological deconstruction of compulsivity

Shifts in the control of behaviour by the goal-directed action system to that of the habitual system tend to be discussed in the literature as a binary: instrumental behaviour is either goal-directed or it is habitual. This is a natural consequence of the way in which goal-directed actions and habits have been operationalised in traditional learning theory discussions: if behaviour is sensitive to outcome revaluation or contingency degradation it is goal-directed, and if it is not then it is habitual. Behaviour is always guided by one or the other. However, such a dichotomy is not a true reflection of how the control of behaviour is actually orchestrated.

Habitual and goal-directed action mechanisms coexist and compete for the control of behaviour. When we discuss the development of habits with progressive training, it reflects a gradual strengthening of stimulus-

response associations over time, and thus a gradual increase in the contribution of the habitual system at the expense of the goal-directed action system, the latter of which correspondingly exerts less control over behaviour. However, the contribution of the goal-directed action system never falls to nil, thus allowing its relative contribution to be radically increased if environmental circumstances change and behaviour needs to be adapted. Likewise, habitual control is likely not entirely absent when behaviours are first learnt, but is simply dwarfed in its relative contribution to the control of behaviour. Stimulus-response associations will form early on, arising contemporaneously with action-outcome associations – stimulus-response and action-outcome learning have been described as occurring in parallel (Everitt and Robbins 2005) – but will be relatively weak to begin with.

The dual control of instrumental behaviour, and its neurobiological basis, by the goal-directed and habitual systems has been elegantly demonstrated in recent experiments by Christina Gremel and Rui Costa and their colleagues, using a within-subject instrumental lever-press task for mice in which random ratio and random interval schedules are used to bias subjects towards goal-directed and habitual control respectively, as well as outcome devaluation to test for the degree of goal-directedness of the behaviour (Gremel and Costa 2013; Gremel et al. 2016). In their first study, the authors demonstrated that neuronal ensembles in the OFC and dorsomedial striatum (DMS) became more engaged during goal-directed behaviour, while neuronal ensembles in the dorsolateral striatum (DLS) became less engaged, and that the magnitude of activity shift in the OFC and DMS correlated with the degree of goal-directedness of behaviour. The OFC was found to mediate switching between control strategies, with its inactivation disrupting goal-directed control and its activation increasing goal-directedness (Gremel and Costa 2013). In their second study, the authors demonstrated that silencing activity in OFC neurons projecting to the dorsal striatum promoted a shift to habitual behaviour (Gremel et al. 2016). They then showed that the attenuation of OFC-DS activity was mediated by endocannabinoid CB1 receptors on OFC-DS projection neurons (Gremel et al. 2016), a result which was in accordance with previous data implicating that habitual control was CB1 receptor-mediated (Hilário et al. 2007).

It is the dual control of behaviour, at any point in time, by the goal-directed action and habitual systems that permits a reinterpretation of the literature on cognitive flexibility. Whilst both reversal learning and contingency degradation are frequently discussed in relation to compulsivity, via the concepts of cognitive flexibility and the balance between goal-directed actions and habits respectively, there is little mention of the other paradigm in basic neuroscience studies and discussions on either subject. An exception is the work of Churchwell et al. 2009, in which the authors discussed their findings of impairments in reversal learning following the separate inactivation of the OFC and amygdala, or their disconnection, in terms of habitual responding. They suggested that

> "subjects with inactivation of OFC cannot flexibly respond to changing contingencies and default to a habit acquired because of overtraining the previous day" (Churchwell et al. 2009).

Whilst I would query the assertion that the experience of a single session's worth of reinforcement under particular stimulus/action-outcome contingencies can amount to "overtraining", the point remains, in my opinion, intriguing and perspicacious.

The OFC helps to mediate a shift between goal-directed actions and habits; the perturbation of its normal functioning results in the dominance of habitual control. That such a role is so rarely mentioned in the many studies reporting OFC involvement in reversal learning is surprising, given how the persistent responding to outdated stimulus/action-outcome contingencies, to the detriment of the animal in terms of reward attainment, has such clear parallels to habits. A recognition of the dual control of behaviour by the goal-directed action and habitual systems, with a greater or lesser contribution of each relative to the contribution of the other, is necessary for such an account to stand. It enables the interpretation that while the control of reversal learning is normally goal-directed, with perturbation of the OFC, the latent stimulus-response associations are utilised in the rise of the relative contribution of habits.

The discussion of OFC perturbation-mediated reversal learning deficits in the context of goal-directed actions and habits is certainly rare, but not non-existent. Torregrossa et al. 2008 also discuss that the involvement of the OFC in encoding action-outcome responses may be responsible for such deficits, as impairment

> "could be considered a failure to devalue the reinforcer (that is no longer presented), which could be interpreted as an increase in habitual responding."

Meanwhile, Talpos and Shoaib 2015 directly equate reversal learning with "overcoming a habit".

The reframing of reversal learning in terms of goal-directed actions and habits requires a more precise specification of the contribution of both types of control to task performance than has been given so far, or has been theorised in the literature. I hypothesise that responding under initial reversal training is mostly controlled by the goal-directed action system. Over time, responding to each set of stimulus/action-outcome contingencies will become more habitual, with the flexible switch between contingencies requiring goal-directed action control, and hence utilising the OFC and caudate. In other words, switching between contingencies is akin to a goal-directed behaviour shifting responding between two different habitual routines. The hypothesis must be elaborated further to take into account the results of chapter 4, in which it was the inactivation of the putamen and not the caudate which impaired reversal learning, regions linked to habitual and goal-directed control of behaviour respectively. Perhaps the switch in responding between sets of stimulus/action-outcome contingencies itself can become habitual with enough training. Supporting evidence for the involvement of habitual control in reversal learning comes from the work of Graybeal et al. 2011, in which mice trained on a reversal task were then exposed to the devaluation of reward and did not alter their responding. Furthermore, lesions of the DLS, in a result directly analogous to that concerning the putamen in chapter 4, were shown to impair reversal performance (Graybeal et al. 2011). Unanswered questions relating to such a theory however are how to explain the data of Groman et al. 2013, and why, if habitual control was impaired, it was only the switch in responding between different contingencies that became dysfunctional, and not responding to each set of contingencies individually. A follow-up experiment which could help to confirm the habitual nature of responding in the task would be to directly apply a test of goal-directed/habitual control of behaviour, such as outcome devaluation as in Graybeal et al. 2011, to overtrained subjects exhibiting putamen inactivation-induced deficits.

However, a new theory of the relationship between cognitive flexibility and habits vs. goal-directed actions also enhances our understanding of compulsivity and OCD. Rather than cognitive flexibility and the balance between goal-directed actions and habits being separate, alternative conceptualisations of compulsivity, they become related interpretations, two sides of the same coin.

6.5 Conclusions

Much of the experimental work in this thesis concerned the neural basis of two popular conceptualisations of compulsivity, cognitive inflexibility and an imbalance between the habitual and goal-directed action systems in the control of instrumental behaviour. These domains were investigated using the paradigms of reversal learning and contingency degradation respectively, with results pinpointing the OFC and putamen in reversal learning, and the OFC and pgACC in contingency degradation, findings which fit neatly with the evidence of abnormalities in these regions as part of the dysfunctional cortico-striato-thalamo-cortical circuitry of OCD.

The findings are not limited in their relevance solely to OCD however. In recent years there has been a burgeoning of interest in dimensional psychiatry, an approach in which researchers attempt to identify core mechanisms of mental disorders across nosological boundaries (Hägele et al. 2015). It is increasingly recognised that our definitions of different mental illnesses are merely formed of clusters of symptoms that tend to associate together, and which may not necessarily map onto the same neuropsychopharmacological substrates. The delineation of simpler traits and constructs, such as compulsivity, which can be combined together to form the intricate symptomatology of a psychiatric disorder has thus become a priority in psychiatric research. It is theorised that it may be easier to uncover the underlying neuropsychopharmacology of such constructs, and then ultimately to discover their genetic basis (Fineberg et al. 2010; Robbins et al. 2012a). It is hoped that the approach will lead to the identification of endophenotypes: objective and quantifiable biomarkers that span the divide between genotype and phenotype of a disorder (Gottesman and Gould 2003; Chamberlain and Menzies 2009; 2012).

The application of constructs such as compulsivity is often found to cross nosological borders. A broad range of psychiatric illnesses have been conceptualised as disorders of compulsivity including not only OCD and the obsessive-compulsive spectrum disorders (Grant and Potenza 2006; Gillan et al. 2011; Gillan and Robbins 2014; Leckman and Riddle 2000; Figee et al. 2015), but also illnesses such as addiction (Robbins and Everitt 1999; Everitt et al. 2001; Everitt and Robbins 2005; Hyman et al. 2006; Everitt et al. 2008; Belin et al. 2009; Hogarth et al. 2013; Everitt 2014; Banca et al. 2016), eating disorders (Godier and Park 2014; 2015; Godier et al. 2016) and schizophrenia (Griffiths et al. 2014; Morris et al. 2015). As such, the findings in this thesis, as well as the rest of the continually evolving body of work that attempts to elucidate the neuropsychopharmacological basis of compulsivity, may not only be part of a paradigm shift in the way that we direct neuropsychiatric research, but may also help further our understanding of multiple illnesses affecting immense numbers of sufferers worldwide.

Appendix A Neuroimaging of OCD

Table A.1. *Resting-state neuroimaging in OCD*

Study	Sample size	Comparison	Region and hemisphere	Finding relative to comparison group
PET				
Baxter et al. 1987	14	Control, Dep	Cerebral hemisphere	↑
			Caudate head	↑
			Orbital gyrus	↑
			L orbital gyrus to L hemisphere ratio	↑
Baxter et al. 1988	10	Control	Cerebral hemisphere	↑
			Caudate head	↑
			Orbital gyrus	↑
			Orbital gyrus to hemisphere ratio	↑
Nordahl et al. 1989	8	Control	Anterior OFC	↑
			R posterior OFC	↑
			Anterior medial	↑
			OFC	↑
			Superior occipital	↑
			Parietal	↑
			L parieto-occipital	↑
Swedo et al. 1989	18	Control	Prefrontal	↑
			L orbitofrontal	↑
			L premotor	↑
			R sensorimotor	↑
			R inferior temporal	↑
			L paracentral	↑
			R cerebellar	↑
			R thalamus	↑
			Anterior cingulate	↑
Martinot et al. 1990	16	Control	Whole cortex	↑
			Prefrontal lateral cortex	↑
Sawle et al. 1991*	6	Control	Orbital frontal	↑
			Premotor	↑
			Midfrontal	↑

continued

Resting-state neuroimaging in OCD (continued)

Study	Sample size	Comparison	Region and hemisphere	Finding relative to comparison group
Perani et al. 1995	11	Control	Anterior cingulate	↑
			Mid cingulate	↑
			L premotor	↑
			R premotor	↑
			L midfrontal	↑
			R midfrontal	↑
Cottraux et al. 1996	10	Control	Superior temporal gyrus	↑
Saxena et al. 2001	17	Control	L thalamus	↑
Kwon et al. 2003	14	Control	R OFC	↑
			L insula	↑
			L inferior parietal	↑
			L parieto-occipital	↑
SPECT				
Machlin et al. 1991	10	Control	Medial-frontal cortex	↑
Rubin et al. 1992	10	Control	OFC	↑
			High dorsal parietal cortex	↑
			Posterofrontal cortex	↑
			Caudate head	↓
Adams et al. 1993	11	-	Basal ganglia	Asymmetric in 8/11 (↓ in 6/8)
Lucey et al. 1995	30	Control	Superior frontal cortex	↓
			R inferior frontal cortex	↓
			L temporal cortex	↓
			L parietal cortex	↓
			R caudate	↓
			R thalamus	↓
Molina et al. 1995	6	Control	R basal ganglia	↑
Lucey et al. 1997a Lucey et al. 1997b	15	Control, PTSD	Superior frontal cortices	↓
			R caudate	↓
Crespo-Facorro et al. 1999	17†	Control	R OFC	↓
Busatto et al. 2000	26	Control	R lateral OFC	↓
			L dorsal ACC	↓
			Cerebellum	↑
Alptekin et al. 2001	9	Control	R thalamus	↑
			L frontotemporal cortex	↑

continued

Resting-state neuroimaging in OCD (continued)

Study	Sample size	Comparison	Region and hemisphere	Finding relative to comparison group
			OFC	↑
Le Jeune et al. 2010	10	Control	R frontal middle gyrus	↑
			R frontal superior gyrus	↑
			R parietal lobe	↑
			Postcentral gyrus	↑
			Putamen	↑
fMRI				
Hou et al. 2012	23	Control	OFC	↑
			ACC	↑
			Cerebellum	↓
			Parietal cortex	↓
Cheng et al. 2013	23	Control	ACC	↑
			Posterior cingulate cortex	↓

[*] Study used ^{15}Oxygen, not FDG.

[†] Includes 6 patients with comorbid motor tic disorder, no differences found between those patients and those with OCD alone.

Findings were bilateral unless hemisphere is given. Sample size given for number of OCD subjects. Dep = depressed patients.

Table A.2. *Symptom provocation neuroimaging in OCD*

Study	Sample size	Region and hemisphere	Finding relative to resting-state
PET			
McGuire et al. 1994	4	R inferior frontal gyrus	↑
		Caudate nucleus	↑
		Putamen	↑
		Globus pallidus	↑
		Thalamus	↑
		L hippocampus	↑
		Posterior cingulate gyrus	↑
		R superior PFC	↓
		Temporoparietal junction	↓
Rauch et al. 1994	8	R caudate	↑
		L ACC	↑
		OFC	↑
Cottraux et al. 1996	10	R ACC	↓
		Thalamus	↓
		Middle orbitofrontal gyrus	↑
		Inferior orbitofrontal gyrus	↑
Rauch et al. 2002	9	R OFC	↑
		Frontal cortex	↑
		L premotor cortex	↑
		L precuneus	↑
Shin et al. 2006	12	L OFC	↑
fMRI			
Breiter et al. 1996	10	Medial OFC	↑
		Lateral frontal	↑
		Anterior temporal	↑
		ACC	↑
		Insula	↑
		Caudate	↑
		Lenticulate	↑
		Amygdala	↑
Adler et al. 2000	7	OFC	↑
		Superior frontal cortex	↑
		dlPFC	↑
		Anterior, medial and lateral temporal cortex	↑
		R ACC	↑
Mataix-Cols et al. 2004*	16	vmPFC (washing)	↑
		R caudate (washing)	↑
		Putamen/globus pallidus (checking)	↑

continued

Symptom provocation neuroimaging in OCD (continued)

Study	Sample size	Region and hemisphere	Finding relative to resting-state
		Thalamus (checking)	↑
		Dorsal cortical areas (checking)	↑
Schienle et al. 2005	10	PFC	↑
		L insula	↑
		R supramarginal gyrus	↑
		L caudate	↑
		R thalamus	↑
Nakao et al. 2005	10	L Frontal cortex inc. OFC & dlPFC	↑
		L temporal cortex	↑
		L parietal cortex	↑
		R cerebellum	↑
Simon et al. 2010	14	L thalamus[†]	↑
		R OFC	↑
		L dlPFC	↑
		L mPFC	↑
		R caudate	↑
		L temporal cortex	↑
		L parietal cortex	↑
		R cerebellum	↑
Sanematsu et al. 2010	17	L superior temporal gyrus	↑
		L precuneus	↑
		Frontal cortices	↑
		R cerebullum	↑
		L temporal cortex	↑
		L parietal cortex	↑
		R cerebellum	↑

[*] Regions found to be related to the now separate disorder of hoarding are not quoted here.
[†] Significant compared to controls, not neutral stimuli vs symptom provocation stimuli.
Findings were bilateral unless hemisphere is given.
Results are compared to resting-state unless otherwise stated.
Findings were bilateral unless hemisphere is given.

Table A.3. *Neuroimaging of neural changes with treatment in OCD*

Study	Sample size	Region and hemisphere	Finding relative to resting-state	Notes
PET				
Benkelfat et al. 1990	8	OFC L caudate R anterior putamen	↓ ⇓ ↑	≥12-weeks clomipramine
Swedo et al. 1992a	13	OFC	⇓	Childhood onset. 10/13 had 1 year of pharmacotherapy
Perani et al. 1995	9	Cingulate cortex	⇓	3 months of fluvoxamine, fluoxetine or clomipramine
Schwartz et al. 1996	9	Caudate Orbital gyrus & caudate head correlation Orbital gyrus & thalamus correlation	⇓ ↓ ↓	10 weeks ERP
Saxena et al. 1999	20	R anterolateral OFC R caudate	⇓ ⇓	8-12 weeks paroxetine
Rauch et al. 2002	10	Posterior cingulate cortex	⇑	12-week fluvoxamine
Hansen et al. 2002	20	R caudate	⇓	≥3 months paroxetine
Kang et al. 2003	9	Lateral & medial OFC R hippocampus Lateral & medial cerebellum R putamen Lateral R postcentral gyrus Posterior superior parietal lobe Medial superior occciptial gyrus	↓ ↓ ↓ ↓ ↑ ↑ ↑	12-week fluvoxamine
Saxena et al. 2009	10	Thalamus R dACC	↓ ⇑	4 weeks intensive CBT.
Apostolova et al. 2010	16	R caudate	⇑	14 ±3.1 weeks paroxetine (n=7) 14 ±4.2 weeks CBT (n=9)

continued

Neuroimaging of neural changes with treatment in OCD (continued)

Study	Sample size	Region and hemisphere	Finding relative to resting-state	Notes
SPECT				
Molina et al. 1995	4	R basal ganglia	↓	4-6 weeks with "serotonergic drug"
Rubin et al. 1995	8	OFC	↑	Clompiramine until symptom reduction (2.1-9.8 months)
		High dorsal parietal cortex	↑	
		Posterofrontal cortex	↑	
Hendler et al. 2003	26	L anterior temporal cortex*	⇑	6 months sertraline
Nakatani et al. 2003†	31	Caudate head	⇓	Behaviour therapy
Diler et al. 2004	18	Caudate	↓	Children. 12 weeks paroxetine
		dlPFC	↓	
		Cingulate	↓	
		R anteromedial temporal cortex	↓	
Carey et al. 2004	14	L superior temporal gyrus	↓	
		Middle frontal gyrus	↓	
		Precuneus	↓	
		R paramedian post-central gyrus	↓	
		L mPFC	↑	
Ho Pian et al. 2005	18	R thalamus	⇓	12 weeks paroxetine
		Putamen	↓	
		Caudate	↓	
fMRI				
Nakao et al. 2005	10	OFC	⇓*	12 weeks behaviour therapy or fluvoxamine
		dlPFC	⇓*	
		ACC	⇓*	
		Parietal cortex	⇑†	
		Cerebellum	⇑†	
Nabeyama et al. 2008	11	Cerebullum	⇑	12 weeks behaviour therapy
		Parietal lobe	⇑	
		OFC	⇓‡	
		Middle frontal gyrus	⇓†	
		Temporal cortex	⇓†	

* Under symptom provocation conditions.
† Study used xenon-enhanced computed tomography to measure rCBF, not SPECT.
‡ During the Stroop task.
Findings were bilateral unless hemisphere is given. Double arrows (⇑ or ⇓) show results which correlated with treatment response.

Table A.4. *Structural MRI studies*

Study	Sample size	Region and hemisphere	Volume/density compared to controls	Notes
Region of interest studies				
Luxenberg et al. 1988	10	Caudate	↓	
Weilburg et al. 1989	1	L caudate head	↓	
Scarone et al. 1992	20	R caudate head	↑	
Robinson et al. 1995	26	Caudate	↓	
Rosenberg et al. 1997a*	21	Corpus callosum	↑	Volume correlated with symptom severity
Rosenberg et al. 1997b*	19	Striatum Third ventricle	↓ ↑	Children. ↓ striatal volume ∝ ↑ symptom severity
Szeszko et al. 1999*	26	Superior frontal gyrus Anterior cingulate gyrus OFC Hippocampus Amygdala	- - ↓ - ↓	
Jenike et al. 1996*	10	Cerebral cortex Cerebral cortex white matter Cerebellar white matter Operculum Thalamus Caudate Putamen Amygdala Hippocampus Insula	↑ ↓ ↑ ↑ - - - - - -	
Choi et al. 2004*	34	Anterior OFC Posterior OFC	↓ (left only) -	
Szeszko et al. 2004a*	23	Globus pallidus Caudate Putamen Anterior cingulate gyrus grey matter Anterior cingulate gyrus white matter Superior frontal gyrus grey matter Superior frontal gyrus white matter	↓ - - ↑ - - -	

continued

Structural MRI studies (continued)

Study	Sample size	Region and hemisphere	Volume/density compared to controls	Notes
Szeszko et al. 2004b*	11	Amygdala	Asymmetry	Children.
Voxel-based morphometry (VBM) studies				
Grachev et al. 1998	10	OFC	-	
		ACC	-	
		Opercular cortex	-	
		Total cerebral neocortex	↑	
Kim et al. 2001	25	L OFC	↑	
		L thalamus	↑	
		L cuneus	↓	
		L cerebellum	↓	
		L superior temporal gyrus	↑	
		L inferior parietal	↑	
		R insula	↑	
		R middle temporal	↑	
		R inferior occipital	↑	
		Hypothalamus	↑	
Pujol et al. 2004	72	Medial frontal gyrus	↓	
		Medial OFC	↓	
		L insulo-opercular region	↓	
		Ventral putamen	↑	
		Anterior cerebellum	↑	
		R amgydala	↓‡	
Valente et al. 2005*	19	L posterior OFC & anterior insula	↑	
		L parahippocampal gyrus & uncus	↑	
		R parahippocampal & fusiform gyri	↑	
		L anterior cingulate & medial frontal gyri	↓	
		R angular & supramarginal gyri	↓	
		R anterior OFC	↓†	
Kopřivová et al. 2009	14	Total white matter	↓	
		Mediofrontal grey matter	↓	
		R temporo-parieto -occipital grey matter	↓	

continued

Structural MRI studies (continued)

Study	Sample size	Region and hemisphere	Volume/density compared to controls	Notes
		R precentral grey matter	↓	
		L middle temporal grey matter	↓	
		L cerebellar grey matter	↓	
		Pons grey matter	↓	
		Mesencephalon grey matter	↓	
Lázaro et al. 2009*	15	Parietal lobe grey matter	↓	Children and adolescents.
	15	Parietal lobe white matter	↓	
Lázaro et al. 2011*	17	Parietal white matter	↓	Adolescents.
Zarei et al. 2011	26	Caudate	↑	
		R putamen	↑	
		R globus pallidus	↑	
Hou et al. 2013	33	L caudate	↑	
		L thalamus	↑	
		Posterior cingulate cortex	↑	
		mOFC	↓	
		L ACC	↓	
		L inferior frontal gyrus	↓	
Tang et al. 2015*	26	R dlPFC	⇓	Adolescents.
		L superior temporal gyrus	↓	
		L precuneus	↓	
		R precentral gyrus	↓	
		L anterior insula	⇑	
		R parahippocampal gyrus	↑	
Treatment-based studies				
Gilbert et al. 2000*	21	Thalamus	↓	Children. 12 weeks paroxetine. ↓ thalamic volume ∝ ↓ symptom severity
Rosenberg et al. 2000*	11	Thalamus	-	Children. 12 weeks CBT.

continued

Structural MRI studies (continued)

Study	Sample size	Region and hemisphere	Volume/density compared to controls	Notes
Szeszko et al. 2004b*	11	L amygdala	↓	Children. 16 weeks paroxetine.
Lázaro et al. 2009*	15	Parietal lobe Parietal white matter	↑ ↑	Children and adolescents. 6 months fluoxetine.

* Computed tomography, not structural MRI.
† Non-depressed patients only.
‡ Patients with aggressive obsessions and checking compulsions only.
Findings were bilateral unless hemisphere is given.

Appendix B Additional Husbandry and Welfare Information

B.1 Housing

Marmosets' cages were custom-made for the laboratory and designed specifically to suit the species (Figures B.1.1 and B.1.2). As far as was possible they were designed to promote species-typical, rather than abnormal, behaviours, the latter of which are a common issue in laboratory environments (Schoenfeld 1989; Garner 2005). Cages for experimental animals measured 280cm height x 120cm width x 73-98cm depth to give a total volume of 2.8728m^3, surpassing the Home Office minimum requirements of 150cm cage height and 0.5m^3 volume. Cages for breeding groups were much larger, in order to accommodate the breeding pair and multiple litters of offspring. Offspring were kept in the breeding groups until ready to be removed and assigned to an experimenter, as older offspring aid rearing of infants and large breeding families of this type simulates the natural group structure found in the wild (Poole and Evans 1982).

Marmosets in the colony were taken out of the breeding pens and paired with another marmoset in an experimental pen when they were ready to be assigned to a researcher (at the age of at least 18 months). In the vast majority of cases partners were of the opposite sex to one another, but occasionally two twin brothers would be placed together if there happened to be more males than females in the colony at that time. The Senior Marmoset Technician and her team took care to ensure that marmosets were behaviourally compatible; marmosets show considerable inter-individual variablility in termperament, which manifests in variability in aggression/timidity and social behaviours (Box 1975). Marmosets were thus selected for pairing on the basis of a similar disposition, and their behaviour monitored closely for any signs of bullying or fighting when first paired, in which event they were immediately separated and repaired with a more suitable individual. Marmosets are generally monogamous (Kleiman 1977, but see Sussman and Kinzey 1984) and are known to form a pair-bond with suitable partners (Evans and Poole 1983; Evans 1983; Gerber et al. 2002), and thus the compatibility of the pair increased the likelihood of successful pair-bonding, promoting positive welfare and the behavioural stability necessary for experimental testing. Research has shown paired housing can form a "social buffer" to stress in non-human primates (Stanton et al. 1985), and marmosets specifically benefit enormously from paired as opposed to single housing, with long periods spent engaged in social behaviours such as allogrooming and huddling (Box 1975), and so were kept in pairs if at all possible. On rare occasions marmosets had to be kept single-housed for short stretches of time however, usually as a result of pairs being separated due to incompatibility, but still had visual, auditory and olfactory contact with other marmosets.

Cages were furnished with poles, ropes and ladders to provide a variety of perches for the marmosets at all vertical levels of the enclosure, as more complex caging promotes more varied behaviours and reduces stereotypy in marmosets (Poole 1990; Kitchen and Martin 1996). As common marmosets are an

arboreal species which routinely utilise the upper parts of enclosures, and are known to flee upwards in a laboratory environment when startled (**Refinements2009**), the top of the cage comprised a clear plastic dome with perches and ropes much higher than human eye-level (Figure B.1.1B), as recommended for the species (Rensing and Oerke 2005). Marmosets slept in nestboxes made of plastic with a wooden floor (Figure B.1.1C), shown to be materials preferred by the species (Rumble et al. 2005). Nestboxes for cannulated animals were adapted to have a flap above the entrance in order to reduce the risk of hitting their cannulae against the nestbox. The cage also contained a veranda with a removable tray (Figure B.1.1D), in which food and sawdust were scattered to encourage natural foraging behaviours seen in the wild (Rylands and Faria 1993). The veranda was positioned high in the cage as this has been shown to be the preferred feeding height for the species (Buchanan-Smith et al. 2002). The floor of the cage was solid and covered with sawdust, again to encourage foraging (Figure B.1.1E) (Chamove et al. 1982; McKenzie et al. 1986; Buchanan-Smith 2010). The cage was mounted on wheels and were thus mobile; every 4-5 weeks the cages were removed and put through a high temperature and pressure cleaning system.

B.2 Feeding regime

Marmosets at the University of Cambridge Marmoset Breeding Colony were given a complex and varied diet which was composed to meet their specific nutritional needs. Animals were raised on a diet which consisted of sandwiches, malt loaf (Soreen Large Fruit Loaf, Soreen, Manchester, UK) rusk, fruit, mealworms, locusts and peanuts (Table B.1; Figure B.2.1) and then switched to a simplified diet when they were issued to a researcher and began to undergo behavioural testing (Table B.3). Marmosets moved to the experimental diet by way of an transitional diet, which they were fed for several weeks in an interim period between the rearing and experimental diets (Table B.2). The weight of the marmosets and their food consumption was carefully monitored during the dietary changes to make sure they adapted well. During breaks in the experiments or any periods of vacation taken by the researcher the marmosets were fed the rearing diet and were taken off water restriction.

Sandwiches were a key part of the diet of animals kept at the colony and are composed of a mixture of boiled eggs, vitamin- and mineral-fortified drink powder (Complan Original Flavour; Nuticia Complan, Wiltshire, UK), Mazuri primate diet powder (Mazuri Callitrichid Gel Diet; Special Diet Services, Essex, UK), multi-vitamin drops (Abidec; Omega Pharma Ltd., London, UK) and vitamin D3 powder (necessary for captive marmosets (Whitehead 1987; Poole 1990; Special Diet Services) in mixed white/wholemeal bread (Hovis Best of Both Medium-sliced Bread; Hovis Ltd.; High Wycombe, UK).

Figure B.1.1. *Homecage and internal furniture. A. Frontal view of a homecage for a pair of experimental animals. B. View of one half of the dome of the homecage, showing pole and rope. C. Frontal view of a nestbox. D. Close view of the veranda, in and on which food was given. E. One of the two sawdust-covered trays that formed the bottom of the homecage.*

Figure B.1.2. *View of the homecage with all four doors open to reveal inner furniture.*

Table B.1. *Feeding schedule for marmosets during rearing.*

Day	Morning	Afternoon
Monday	Maltloaf	Rusk and pear
Tuesday	Sandwich	Peanut and banana
Wednesday	Sandwich	Rusk and apple
Thursday	Mealworms	Peanut/locusts and grapes
Friday	Sandwich	Rusk, pear and forage mix
Saturday	-	Sandwich and banana
Sunday	-	Sandwich and apple

Table B.2. *Feeding schedule for marmosets during transition to experimental diet.*

Day	Morning	Afternoon
Monday	Maltloaf	Rusk and pear
Tuesday	Sandwich	Peanut and banana
Wednesday	Sandwich	Rusk and apple
Thursday	Mealworms	Peanut/locusts and grapes
Friday	Sandwich	Rusk, pear and forage mix
Saturday	-	Sandwich and banana
Sunday	-	Sandwich and apple

Table B.3. *Feeding schedule for marmosets during experiments.*

Day	Morning	Afternoon
Monday	-	Pellets and orange
Tuesday	-	Pellets and carrots
Wednesday	-	Pellets and carrots
Thursday	-	Pellets and carrots
Friday	-	Sandwich, rusk, pear and forage mix
Saturday	-	Sandwich and banana
Sunday	-	Pellets and carrots

Figure B.2.1. *Marmoset diet. A. Subject eating a piece of pear. B. Subjects foraging for food on the veranda. Forage mix was interspersed with sawdust and marmosets had to find pieces and fish them out through a metal grid. C. Subject eating a grape. D. Rusk. E. Orange segments. F. Grapes. G. Marmoset sandwiches. H. Carrot. I. Pear. J. Peanuts within their shells. K. Apple. L. Forage mix, outline shows portion for two marmosets. M. Pellets, outline as for L. N. Banana. O. Malt loaf.*

B.3 General welfare monitoring

Marmosets were monitored closely for any negative welfare indicators, which included weight loss (see below), a huddled posture with lowered head, reduced locomotion, reduced approach for food, reduced interation with partner and piloerection, by the researcher, NACWO, NVS and the Senior Marmoset Technician and her team. In particular, the researcher and technicians interacted with the marmosets on a daily basis and grew to know their individual patterns of behaviour, and thus any ailments inducing behavioural change were detected quickly. Marmosets were susceptible to a variety of ailments unconnected to their participation in experiments including gastrointestinal upset, gum infection, pulled nails and minor cuts, as well experiment-specific issues of poor recovery from surgery or complications, i.e. bleeding or infection, at the cannula wound site. These problems were brought to the attention of the NACWO and NVS and treated appropriately, with the oral administration of the antibiotics enrofloxacin (Baytril 2.5% oral solution; Bayer plc., Berkshire, UK; 0.1 ml/day of 25 mg/ml solution for seven days) or clavulnate-potentiated amoxicillin (Synulox; Zoetus UK Ltd., London, UK; 0.25 ml/day of 40 mg/ml solution for seven days) if necessary.

B.3.1 Condition score and weight monitoring

Marmoset weight loss during experiments was regarded as a serious negative welfare indicator and was carefully monitored, with marmosets being weighed on a weekly basis when participating in any kind of testing, or when on any diet other than the rearing diet (Figure B.3.1). In the event that marmosets were on the rearing diet and not being tested they were weighed monthly. It was recognised however that weight was not a useful measure in isolation, and weight was thus considered in the context of the overall condition of the animal, in a process called condition scoring. In condition scoring, the muscle tone and fat distribution of the marmoset was considered in three key areas: the leg, pelvis and spine (Table B.4). In order to ascertain the individual baseline to which the weekly weights of each marmoset should be compared, marmosets underwent a process to find a healthy "start weight" prior to their being issued to a researcher and being used in any experiments. To find their start weight, marmosets were moved from the rearing diet to the experimental diet and their condition score monitored. Given that marmosets were often overweight in the breeding pens, most animals lost weight during this time, and they were kept on the experimental diet until their overall condition score was in the optimal range of 3-4 (normally a period of 2-3 weeks). At the point at which the marmosets achieved this healthy condition score, their weight was noted and taken to be the start weight.

Weight loss that was considered to be larger than normal fluctuations (>20g in a week) or weight loss that brought an animal's weight below 90% of their start weight was reported to the NACWO and induced closer monitoring of the marmoset and potentially dietary changes. Weight loss of 10% of start weight was also recorded as an adverse effect. Weight loss of 20% or more with a decline in condition score was considered a humane endpoint (Stokes 2002; Morton 1998) and marmosets would be euthanased.

Figure B.3.1. *Subject being weighed in carrybox.*

Table B.4. *Condition scoring assessment. Fat distribution and muscle tone were assessed according to the criteria above and scores chosen for the leg, pelvic and spinal regions. The three scores for each area were then averaged to give an overall condition score for the animal.*

Condition score grade	Leg muscle	Pelvis	Spine
1	No muscle tone, very small, no definition, bone easily palpatable	Very easy to palpate, no muscle/fat cover, clearly visible	Can palpate spinous and transverse processes of vertebrae, spine visible
2	Poor muscle tone, small, no definition	Easy to palpate, some muscle/fat cover, visible	Can palpate spinous processes very easily, and transverse processes with pressure, some fat pad between the two
3	Average muscle tone, average size, clearly defined	Able to palpate with pressure, good muscle/fat cover, not visible	Can palpate spinous processes easily and transverse processes with firm pressure, reasonable fat pad between the two
4	Excellent muscle tone, large, clearly defined	Able to palpate tips of pelvis only, good muscle/fat cover	Can palpate the spinous processes with firm pressure, transverse processes difficult to feel
5	Poor muscle definition due to excessive fat	Difficult to detect pelvis due to excessive fat	Difficult to feel spinous and transverse processes

B.3.2 Anaesthesia and analgesia

As previously described, anaesthesia was induced by injection of ketamine i.m. and continued by the administration of vaporised isofluorane/O_2 via intubation (§2.4.1 and 2.4.2), a combination which is recommended for marmosets (Unwin 2005). Ketamine has been found to be suitable for use with non-human primates, with a wide margin of safety, but is considered insufficient to be used alone in terms of blocking pain (Eisele 1990). It is thought to provide improved surgical anesthesia, analgesia and muscle relaxation when used in combination with other anaesthetics however (Eisele 1990). We have found it very effective in the laboratory, as animals are quickly and easily made unconscious, and thus the pre-surgical preparations and intubation can be made without the use of physical restraint. The use of inhalant anaesthetics such as isofluorane are recommended for laboratory use as they give a high degree of control over the anaesthetic depth, as well as a more rapid recovery from anaesthesia as the isofluorane can be cleared rapidly from the animal by exhalation (Eisele 1990; Martin et al. 2014; Authier et al. 2006). Isofluorane has been shown to induce more hypotension (Martin et al. 2014) and hypothermia (Authier et al. 2006) than other agents in macaque studies, and so these factors are monitored carefully during surgery. Anaesthetic was administered with according to the principle that the lowest levels that provide suitable anaesthesia should be used, to prevent unnecessary cardiovascular depression and to promote faster recovery (Eisele 1990).

Analgesia was provided for at least three days post-operatively, as well as pre-operatively, regardless of the exhibition of any signs of pain or distress from the marmosets, which were normally absent. Analgesia was thus given according to the principle that pain relief should be provided not only in response to signs from the animal, but also prophylactically at times when pain could reasonably occur, but without waiting for it to manifest, in order to minimise suffering (Spinelli 1990; Benson et al. 1990). Prophylactic analgesia after surgery also helped overcome the difficulty that pain might not result in obvious signs in animals, and can be difficult to detect (Carstens and Moberg 2000).

B.3.3 Adverse effects

Several adverse effects occurred in the course of the studies which form this thesis, all of which were treated in conjunction with the NACWO and NVS. Five marmosets showing greater than 10% weight loss, which was then regained, at some point during behavioural testing, and the cannulation site of one marmoset developed an infection which was successfully treated with antibiotics. Four marmosets showed signs of swelling of the wound site or neck after surgery, and so their neckchains were removed for several days and in two cases additional analgesia given. The cannula of one animal was bent by its partner, but was readily fixed without the use of anaesthesia, and metal caps were put into place to prevent a recurrance of the incident. Two animals removed their stitches after surgery, were resutured under anaesthesia, and given another full course of analgesia. In one animal, Subject 2a, the dental cement mount of the cannula was cracked after he had completed the study. Subject 2a showed no signs of distress, but was at risk of the cannula becoming loose, and so was euthanased immediately. As already described, one marmoset of the nine which received 5,7-DHT OFC lesions showed seizure activity in the form of a spinal tremor and/or head twitching, which were successfully treated with oral and/or injectable diazepam. One marmoset

exhibited some paralysis in a hind limb following surgery; they were considered to have reached a humane endpoint and were euthanased.

B.4 Identification

All marmosets were given names as infants under which all their records were kept. To allow easy identification in the cage by those not familiar with the individuals in question, they wore neckchains threaded wth a medallion (Figure B.4.1A); each medallion was inscribed with a unique identifying number which was also present on all records. The neckchains were put on the marmosets when they reached ~12 months old and their length adjusted if necessitated by growth or weight gain. Before the age of 12 months old, juvenile marmosets were identified from each other in the breeding group by shaving a portion of the tail.

Inkeeping with Home Office regulations, each cage contained a card with the names and numbers of each marmoset, for ease of identification. Experimental monkeys each had their own card comprising their name, number, dietary instructions, the name of the personal licence holder and their PIL number, and the relevant study plan code (Figure B.4.1B).

Figure B.4.1. *Identification of experimental monkeys. A. Subject with visible neckchain and numbered medallion. B. Cage card with husbandry and legal information (experimenter details blacked out for reasons of privacy).*

B.5 Assignment of animals to experimental groups

Marmosets within the colony were assigned to specific researchers and studies on the basis of a behavioural screening protocol conducted by the Senior Research Technician, which all experimental marmosets underwent following their removal from the breeding pens and pairing, and condition scoring. The behavioural screening comprised two non-invasive and widely used assessments of anxiety and fear: the human intruder (**Peterson2015**; Kalin and Shelton 1989; Shackman et al. 2013) and snake tests (Barros et al. 2002; Izquierdo and Murray 2004; Clara et al. 2008).

In the human intruder test, a marmoset is divided from their partner and exposed to an unfamiliar human who stands in front of their cage and stares at them for a regulated period of time (Figure B.5.1). The unfamiliar person could potentially engage with the marmoset in positive or aversive ways, such as giving food or catching, and thus an ambiguous and mildly threatening situation is created. In the snake test, the marmosets were again divided from their partners and exposed to a rubber model of a snake, an inherently fearful stimulus, in positioned in a corner of the cage (Figure B.5.1). Marmosets vary greatly in their reactivity to the intruder or snake, showing a range of levels of approach, vocalisations and coping behaviours such as body bobbing. The tests are videoed and analysed to create a component score for each which takes the full range of behaviours. Both tests have been well-validated in the laboratory (Agustín-Pavón et al. 2012; Shiba et al. 2014; 2015; Mikheenko et al. 2015) and high scores are thought to reflect high trait-like anxiety (Shiba et al. 2016; 2014; Mikheenko et al. 2015; Oikonomidis et al. 2016). Marmosets selected for my experiments generally had low human intruder and snake scores, as low anxious marmosets were trained more readily on the touchscreen.

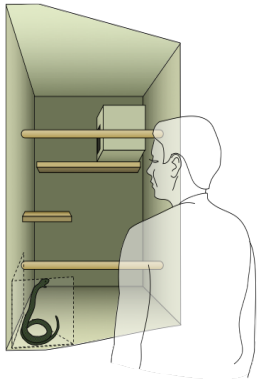

Figure B.5.1. *Illustration of human intruder and snake tests. Figure taken from Oikonomidis et al. 2016, with specific figure credit to Yoshiro Shiba.*

B.6 Cannula cleaning

All cannulated marmosets underwent a dummy and cap change, and a cleaning of the cannulation site every 1-2 weeks. The procedure was developed in response to the development of a series of infections, mostly of a low-level surface nature, in a subset of cannulated marmosets in the laboratory, with the aim of reducing the incidence of such infections. Marmosets were caught and held in the same manner as for an infusion (§2.5.1) and taken to the infusion room. Their caps and dummy cannulae were removed, with the use of forceps if necessitated by dense guide cannula placement. The top of the guide cannula was cleaned with a 70% ethanol wipe and fresh sterile dummy injectors and caps were inserted. Cotton buds soaked in 70% ethanol solution were then used to wipe around the dental cement, with a particular focus on area where the skin met the cement.

B.7 Environmental enrichment

Environmental enrichment, defined as"changing the animal's environment in such a way that the animal voluntarily becomes more active than it was, and there is a measure of reduction or elimination of abnormal behaviour" (Spinelli 1990), is now widely recognised to be a critical part of positive welfare maintenance for laboratory animals (Newberry 1995; Bayne 2003; Vitale and Manciocco 2004; Lutz and Novak 2005; Nelson and Mandrell 2005; Tarou and Bashaw 2007; Baumans and Van Loo 2013), and has been shown to reduce aggression and abnormal behaviours in captive non-human primates (Honess and Marin 2006). Standard cage furniture can be chosen to provide environmental enrichment: marmosets frequently scent mark their surroundings in the wild (Lacher et al. 1981; Lazaro-Perea et al. 1999), and cages were designed with internal cage furniture made of wood, the optimal material for gnawing and absorbing scent mark secretions (Layne and Power 2003) (Figure B.7.1A, B). As well as permanent poles and perches, temporary poles were used to add novelty (Figure B.7.1E). Food-based devices have been shown to be most popular form of enrichment with marmosets (Poole 1990; Majolo et al. 2003), and the Senior Marmoset Technician and her team regularly constructed devices for the marmosets which were given to them after behavioural testing. Lickers were formed of a sealed container filled with blackcurrant juice, into which a ridged stick was inserted through a small hole. By moving the ridged stick in and out of the hole the marmosets could extract small amounts of blackcurrant juice at a time (Figure B.7.1C, D). Another successful enrichment device a mealworm foraging box, reminiscent of mealworm and puzzle feeders already described in the literature (Roberts et al. 1999; Vignes et al. 2001; Rosa et al. 2003). A cardboard box was filled with mealworms interspersed through shredded paper and holes cut in the outside. The marmosets reached through the holes in the cardboard to forage for mealworms (Figure B.7.1F). An additional benefit of the device was that the marmosets could destroy the cardboard box afterwards, another recommended form of enrichment (**Refinements2009**). Marmosets were also often provided with exotic fruit kebabs; pieces of exotic fruit which were not part of the standard diet would be threaded through string and placed in a part of the cage where marmosets had to work to access them (Figure B.7.1G).

Figure B.7.1. *Examples of enrichment. A. Subject scent marking. B. Pole with evidence of gnawing and scent marking. C, D. Subjects using lickers. E. Subjects using a hanging pole, added to the cage temporarily. F. Subject using a puzzle feeder-like enrichment device. G. Subject eating a fruit kebab.*

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